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Exploring the effect of dopaminergic medication on recognition memory in idiopathic Parkinson's disease: Trials and Challenges.

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Abstract

Parkinson's disease (PD) is caused by the degeneration of dopaminergic cells in the substantia nigra (SN) and ventral tegmental area (VTA) of the midbrain. Until recently, PD research predominantly focused on motor symptoms which are synonymous with the condition. Along with the acknowledgment that PD is no longer considered a 'motor disorder', there has been a significant increase in research designed to increase the understating of the nature, origins and management of a range of nonmotor symptoms, which can accompany a PD diagnosis.

Investigations into a frequently reported memory decline in PD, have largely neglected to account for the influence of dopamine replacement therapies on such decline and specifically, the impact of second generation, non-ergot derived, D2 agonists, ropinirole and pramipexole have yet to be explored.

In a between groups comparison, 2 clinically matched subgroups of PD patients, 1 medicated with ropinirole and the other with pramipexole were administered a test of recognition memory, familiarity and recollection on two separate occasions, once in a medicated state and once after a period of withdrawal. Results revealed that when in a medicated state, the PD subgroup medicated with pramipexole exhibited a significantly poorer recollection performance than the subgroup medicated with ropinirole. Furthermore, recollection significantly improved in the subgroup medicated with pramipexole when tested after a period of withdrawal, whilst ropinirole had no effect on memory performance. These findings suggested for the first time that pramipexole may induce a recollection impairment in PD. However, with the between groups methodology employed in this study, 3 possible scenarios remain as potential explanations of these findings; a PD phenotype, characterized by a memory decline, for which pramipexole is a only a marker based on its effectiveness in alleviating tremor and depressive symptoms; an drug effect, the high binding affinity that pramipexole has for d3 subreceptors, prevalent in the hippocampus, disrupts hippocampally dependent episodic memory processes, whereas ropinirole does not by virtue of a broad spectrum binding affinity for d2/d3/d4 subreceptors; a phenotype*drug interaction, a synthesis of the other 2

scenarios, where a PPX phenotype has a memory deficit which is particularly vulnerable to further impairment induced by pramipexole.

To investigate these findings further, a fully powered, randomised controlled, crossover trial is required, whereby a PD cohort usually medicated with either ropinirole or pramipexole are combined and subsequently tested on each drug. A pilot trial was conducted to show how analysis could investigate the 3 scenarios described above, to obtain recollection estimates for a power calculation and to validate a battery of neuropsychological assessments to inform the design of a fully powered trial. Furthermore, recall measures were used and their relationship with recollection assessed to identify a clinically accessible test that could be administered in a clinical environment that is simpler and quicker to complete than a recollection assessment based on the remember/know paradigm.

Throughout the duration of the pilot trial, recruitment was a major challenge. To explore this, eligible PD patients who declined to participate - and their caregivers - were interviewed to explore their perceived barriers to participation in clinical trials. A thematic analysis revealed four themes (*switching medication, trial accessibility, fear of the unknown and caregiver workload*) and several sub themes which represent decliner's primary concerns.

The findings presented in this thesis, contribute to current understanding of how memory is affected in PD, not just by the disease pathology but by dopamine replacement therapies. Findings have implications for dopaminergic modulation of hippocampal processes literature. Potential mechanisms for the dopaminergic disruption of glutamatergic and cholinergic modulation of hippocampal processes and the adequacy of the dopamine overdose model in accounting for acute dopamine therapies and the clinical management of PD are discussed. Furthermore, a number of recommendations are made to reduce perceived barriers to recruitment when designing and managing drug trials, not just with PD patients, but other clinical populations.

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1. Chapter 1: An introduction to Parkinson's disease.

1.1. Parkinson's disease

Parkinson's disease (PD) has a prevalence 0.3% in the general population but around 1% in those over 60 years of age (Rajput, 1992; de Rijk, Laurer, Berger et al., 2000). There are an estimated 6.3 million people with PD worldwide, 1.5 million in Europe and over 127,000 in the UK and these numbers are expected to rise expected to rise with the increasing life expectancy of the worldwide population which will have significant economic, social and health care planning implications (Lindgren, von Campenhousen, Spottke, Siebert, & Dodel, 2005; de Rijk et al., 2000). The incidence of PD increases with age – from 21 cases per 100,000 between the aged 55 to 59 years to 44 cases per 100,000 in individuals aged 60-64 (Twelves, Parkins, & Counsell, 2003). Men are reported to be slightly more vulnerable to the development to PD (Van Den Eeden et al., 2003; Baldereschi, Di Carlo & Rocca, 2003). The age of onset is usually between the late 50s and early to mid-60s, although in early onset Parkinson's symptoms can develop between 21-40 years of age (Muthane, Swamy, Satishchandra, Subhash, Rao & Subbakrishna, 1994).

1.2. Pathophysiology and Neuropathology

The clinical hallmark of PD is the degeneration of dopaminergic cells in the substantia nigra pars compacta (SNPc) and ventral tegmental areas (VTA), resulting in a progressive reduction in dopaminergic innervation in the basal ganglia (Hornykiewicz, 1966). Typically, a loss of more than 30% of nigral dopaminergic neurons and 80% loss of putamen dopaminergic content is required for the manifestation of clinical symptoms which may include tremors, postural instability, rigidity and bradykinesia (Cheng, Ulane, & Burke, 2010; Nandhagopal, kuramoto, Schulzer, Mak, Cragg, McKenzie et al., 2010; Hornykiewicz, 1998; Fearnley & Lees, 1991). These motor symptoms have a significant negative impact on quality of life reported in PD patients (Rahman, Griffin, Quinn & Jahanshahi, 2008).

1.3. Why study nonmotor symptoms in PD?

In James Parkinson's original conception of the condition in 'An essay on the Shaking Palsy (1817), Parkinson describes the 'senses and intellect as being uninjured' was originally viewed as a pure motor disorder. More recently, the nonmotor symptoms of PD have become much more prominent as evidence increasingly shows the importance of the nonmotor symptoms on patient reported quality of life, rates of institutionalisation and health economics (Chaudhuri, Healy & Schapira, 2006). However, despite this, the nonmotor symptoms of PD are still inadequately recognised and consequently poorly treated (Sullivan, Ward, Hauser & Zesiewicz, 2007). Autonomic dysfunction, cognitive abnormalities, sleep disorders, mood disorders, pain and sensory disorders, there also a range of nonmotor symptoms which manifest in PD patients as a result of their pharmacological treatment. The most commonly reported nonmotor symptoms are presented in Table 1 (adapted from Sung & Nicholas, 2013) below. The traditional, pathophysiological explanation of PD is inadequate to explain the development of the nonmotor symptoms. As PD reflects abnormalities in several other neurotransmitters such as brainstem acetylcholine, noradrenaline and serotonergic systems (Halliday, Lees & Stern, 2011; Chaudhuri & Schapira, 2009; Fox, Brotchie, & Lang, 2008; Chaudhuri, Healy & Schapira, 2006).

Table 1

The nonmotor symptoms experienced in Parkinson's disease.

Category	Subcategory	Examples
Autonomic dysfunction	Gastrointestinal dysfunction	Constipation Sialorrhea/drooling Fecal incontinence
	Genitourinary dysfunction	Urinary urgency/frequency Urinary incontinence Sexual dysfunction
	Cardiovascular dysfunction	Orthostatic lightheadedness/ hypotension Dyspnea on exertion Fatigue
Cognitive dysfunction		Bradyphenia Executive dysfunction PD dementia Memory failure
Sleep disorders		REM sleep behaviour disorder Restless leg syndrome Vivid dreaming Periodic limb movements of sleep Excessive daytime somnolence Insomnia
		Depression Anxiety/panic attacks Apathy
		Parethesias Limb pain Joint pain Visceral pain
Pain and sensory disorders	Pain	Loss of sense of smell Obsessive-compulsive behaviours
	Olfactory dysfunction	Visual hallucinations Delusions Illusions
	Impulse control disorders	
NMS secondary to pharmacology	Psychosis	

Notes and Abbreviations. NMS, nonmotor symptom; REM, rapid eye movement

The cellular mechanisms which precipitate the development of these symptoms are complex and include dopaminergic, brainstem acetylcholine, noradrenaline and serotonergic systems (Halliday, Lees & Stern, 2011; Chaudhuri & Schapira, 2009; Fox, Brotchie, & Lang, 2008; Chaudhuri, Healy & Schapira, 2006), however many nonmotor symptoms not only occur in advanced stages of PD, but prior to the clinical manifestation of the motor symptoms which are more synonymous with

the condition (Lang, 2011). Therefore investigation of nonmotor symptoms is essential not only to increase early diagnosis of PD, to improve the clinical care and quality of life of PD patients but also to develop understanding of the aetiology and course of such symptoms (Chen, Zhao, Zhang, Lu, Liu, Huang et al., 2015).

1.4. Treatment

There are a number of treatment options for the management of PD, including pharmacological therapies, surgery and supportive therapies, such as physiotherapy and occupational therapy. Treatments target the symptoms of PD – primarily the motor symptoms and are geared towards replacing depleted levels of dopamine. There are currently no treatments available which have been shown to slow down the progression of PD or to prevent its clinical manifestations (Oertel & Schulz, 2016). Clinical guidelines recommend that once a PD diagnosis is confirmed and the severity of motor, sensory, autonomic and psychiatric symptoms have been assessed, a therapeutic plan should be developed which is individualised to each patient (Jankovich & Stacey, 2007).

1.4.1. Levodopa

Levodopa (l-dopa) is the metabolic precursor of dopamine, but unlike dopamine, l-dopa crosses the blood-brain barrier and is taken up by the nigral-striatal neurons by an enzyme called aromatic amino acid decarboxylase (AADC). Dopamine is stored in vesicles in the presynaptic neuron from where it is released into the synaptic cleft (Thanvi & Lo, 2003). As a neurotransmitter, dopamine acts on postsynaptic dopamine receptors and is metabolised by the reuptake enzymes monoamine oxidase B (MaoB) and catecholamine-o-methyltransferase (COMT) see section 1.4.3. One of the major challenges of l-dopa treatment for PD patients is maintaining an 'on' or medicated state. With the loss of dopaminergic terminals in the striatum, the brain's capacity to store and transfer l-dopa is compromised and consequently shortens the half-life of l-dopa treatment, this

results in a 'wearing-off' effect and an increase in symptom severity (Verhagen, Konitiotis & Chase, 2000). In addition, a delay in achieving an 'on' state is often experienced by patients, particularly in severe PD where the degeneration of striatal dopaminergic terminals is more pronounced. Blindauer (2003) reported that a delay in achieving an 'on' state accounted for the reported 60% of 'off' time experienced by 327 patients with advanced PD.

To increase the duration of the treatment effects of l-dopa and of the remaining endogenous levels of dopamine in the synaptic cleft, l-dopa is often accompanied with a MaOB inhibitor (rasagiline, selegiline) or a COMT inhibitor (Entacapone/Tolcapone). Whilst l-dopa preparations may be the most efficacious of all the dopaminergic therapies, the majority of PD patients exhibit motor complications such as dyskinesias (involuntary movement) after approximately 5 years of treatment (Jankovic, 2005). Dosage level and duration of l-dopa treatment are the major risk factors for these complications and as a result, the initiation of l-dopa therapy is typically delayed by treating physicians in order to delay the onset of l-dopa-related complications (Jankovich, 2002b).

1.4.2. Dopamine agonists

To delay the initiation of l-dopa treatment and the associated treatment related dyskinesias, dopamine agonists (DAs) are used as the starting treatment for many PD patients and whilst the DA monotherapy effects may be small, it is enough to delay l-dopa treatment. DAs are also frequently used as adjunctive therapy to l-dopa (Nohria & Partiot, 1997; Quinn, 1995).

Initially, ergot-derived DAs (bromocriptine, lisuride, cabergoline and pergolide), were more commonly used in clinical practice, however the use of these traditional DAs has significantly reduced with evidence of their association with peptic ulcer disease, vasoconstrictive effects, erythromelalgia and cardiovascular events (Roth 2007; Zanettini, Antonini & Gato, 2007; Tintner, Manian & Gauthier, 2005). As a result, second generation, non-ergot derived dopamine agonists

(pramipexole, ropinirole, rotigotine and apomorphine), particularly, ropinirole and pramipexole are now more commonly used (Wishart & MacPhee, 2011).

DAs mainly act directly on the postsynaptic receptor, not requiring presynaptic synthesis and therefore mimicking endogenous dopamine (Jankovic & Aguilar, 2008). Pramipexole has been associated with a reduction in daily l-dopa dose of approximately 25%, and a potential neuroprotective effect (Albrecht & Buerger, 2009; Zou, Jankovic, & Rowe 1999). Ropinirole has been shown to be effective in controlling the motor symptoms in early and advanced PD, although doses of up to 24mg a day may be required to achieve optimal symptoms control (Korcyn, Thalamas & Adler, 2002). A meta-analysis provided evidence of the comparable efficacy of ropinirole and pramipexole in controlling the motor symptoms of PD, with equivalent risk of dizziness, nausea or hypotension, either as monotherapy or as adjunct to l-dopa (Etminan, Gill & Samii). The impact of DAs on the non-motor symptoms of PD are much less understood, but are of particular interest as evidence has suggested their association with pathological gambling and compulsive behaviours (Dodd, Klos, Bower, Geda, Josephs & Ahlskog, 2005; Driver-Dunkley, Samanta & Stacey, 2003). The effect of ropinirole and pramipexole on cognition and in particular recognition memory is very much under explored.

1.4.3. Monoamine oxidase B (MaoB-I) and catecholamine-o-methyltransferase (COMT) inhibitors

To prolong the dopamine response in PD, l-dopa treatment is often supplemented with an adjuvant enzyme inhibitor. MaoB-Is like selegiline and rasagiline inhibit the release of the enzyme monoamine oxidase into the synaptic cleft which breaks down dopamine and therefore reduce l-dopa dosage by up to 30% (Oertel & Quinn, 1996). COMT inhibitors, such as entacapone, work by reducing catechol-o-methyltransferase-mediated metabolism of dopamine, therefore increasing the duration of available dopamine and can reduce the daily l-dopa dose by over 25% (Grandas & Hernandez, 2007; Munchau & Bhatia, 2000)

1.4.4. Amantadine and N-methyl-D-aspartate (NMDA) antagonists

In PD patients with dyskinesias, amantadine, a N-methyl-D-aspartate (NMDA) antagonist, has been suggested to modestly reduce these motor complications, without exacerbating other PD symptoms (Rajput, 1997; Verhagen, Metman & Del Dotto, 1997). However, a Cochrane meta-analysis of randomised controlled trials to treat motor complication in PD with amantadine, suggested there is insufficient evidence of its treatment efficacy (Crosby, Deane & Clarke, 2003). An alternative NMDA antagonist, dextromethorphan, has been shown to reduce motor complications when used as an adjunct therapy with L-dopa (Blanchet, Metman & Mouradian, 1996).

1.4.5. Non-pharmacological Treatment (Deep Brain Stimulation)

Deep Brain Stimulation (DBS) of the ventral intermediate nucleus (VIM), substantia nigra (STN) and internal Globus Pallidus (GPi) has been developed for the treatment of the motor symptoms of PD to specifically target motor fluctuations (STN, GPi) and for resting tremor that is resistant to dopaminergic therapies (VIM, STN) (Oertel & Schulz, 2016). Motor fluctuations in PD patients occur when patients transition from an 'medicated' state, as a result of effective dopaminergic treatment, to an unmedicated state (or reducing medicated state) as a result of insufficient levels of dopamine in the Central Nervous System (McIntyre & Anderson, 2016). STN stimulation through DBS typically leads to at least a 50% reduction in medication usage, consequently the neuropsychiatric symptoms secondary to dopamine therapy, and other medication side effects are significantly reduced. DBS is the most effective way to treat motor symptoms over any available pharmacological treatment, particularly if patients are carefully chosen (Deuschl, Schade-Brittinger, & Krack, 2006; (Deuschl, Schubach, Knudsen, Pinkser, Cornu, Rau, Agid & Schade-Brittinger, 2013) however the impact of DBS on nonmotor symptoms is unclear and no protective efficacy against further disease progression has been evidenced (Oertel & Schulz, 2016).

1.4.6. Non-motor symptoms and dopaminergic therapy

The evidence base for the treatment of non-motor symptoms is poor (Chaudhuri, Healy & Schapiro, 2006) and in a review of the pharmacological and non-pharmacological treatments for nonmotor symptoms in PD, the Movement Disorder Society Task Force suggested there is insufficient evidence for the treatment PD nonmotor symptoms with dopaminergic therapy (Goetz, Poewe, Rascal & Sampario, 2005). In a more recent review, Wishart and MacPhee (2011) suggested that perhaps the most effective way to manage some nonmotor symptoms through dopaminergic therapy may be through the optimisation of current dopaminergic regimen dosage. Open label and blinded studies indicate pramipexole as a treatment option for depressive symptoms, whilst controlling for motor symptom improvement, however it has also been reported that both pramipexole and ropinirole treatment can also lead to experiences of mania (Singh, Althoff, Martineau & Jacobsen, 2005; Rektorova, Rektor & Bares, 2003). Imaging evidence suggests there is reduced cholinergic activity in PD (Bohnen, Kaufer, Ivancov, Lopresti, Koeppe, Davis et al., 2003), and therefore cholinesterase inhibitors may have a beneficial effect on cognitive symptoms in PD with dementia, visual hallucinations, patients with co-morbid behavioural disorders and psychosis (Burn, Emre, McKeith, DeDy. Aarsland, Hsu et al, 2006; Aarsland, Mosimann & McKeith, 2004). However, this effect was not found in all PD patients, and frequent, significant side effects were experienced, such as extreme tremor and vomiting. Other cholinergic agents, rivastigmine and donepezil have been shown to reduce memory impairments in small groups of PD patients (Ravina, Putt, Siderowf, Farrar, Gillespie, Crawley, 2005; Emre, Aarsland, Albanese, Byrne, Deuschl, De Dyn et al, 2004; Leroi, Brandt, Reich, Lykestos, Grill, Thompson et al, 2004). Furthermore, memantine (an NMDA antagonist) has also been shown to improve memory performance in PD patients with dementia (Aarsland, Ballard, Walker, Bostrom, Alves, Kossakowski et al, 2009b). Effective ways to treat the cognitive symptoms in PD patients without dementia requires further work.

1.5. Genetics

Over the last 15 years PD-linked genes or PD risk factors have been identified by gene mapping which locates genes underlying the development of PD (Thomas & Beal, 2007). Six genes have been shown to have unequivocal links to the heritability of PD. Mutations of SNCA (PARK1) and LRRK (PARK8) are linked to autosomal-dominant forms of PD – whereby a single allele mutation of the gene is enough to cause PD. Parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7) and ATP13A2 (PARK9) suggest an autosomal recessive mode of inheritance where 2 mutations are required (Klein & Westernberger, 2012). Research has identified subtle differences in the presentation of symptoms in particular genetic forms of PD, for example, PARK2 and PARK8 are associated with a higher risk of l-dopa-related motor related complications (Schrag & Schott, 2006; Lucking, Durr & Bonifati, 2000). No formal guidelines have been developed by the Movement Disorder Society or other PD affiliated group about who should be tested, and when, to enhance knowledge and understanding of genetic risk factors in PD. Genetic forms of PD are rare in contrast to idiopathic variants approximately 10% of patients report a positive familial link (Thomas & Beal, 2007). However, genetic research is crucial to developing a better understanding of the pathophysiology and symptoms of PD as well as enabling early identification of those at risk of developing PD.

1.6. Imaging

Commonly used imaging techniques in PD include Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). Magnetic resonance imaging (MRI) is rarely used as a diagnostic aid as the diagnosis of PD is typically based on the patient's presentation (and response to dopaminergic therapy) and not the identification of imaging biomarkers (Pyatigorskaya, Gallea Garcia-Lorenzo, Vidailhert & Lehericy, 2014). MRI has been used to assess structural changes in PD, and has been particularly useful in identifying differences between PD with and without dementia and the origins of memory deficits, and risk factors for dementia development, from PD or PD MCI (Ibarretxe-Bilbao, Ramírez-Ruiz, Tolosa, Marti, Valldeoriola, Bargello, et al., 2008; Bouchard,

Malykhin, Martin Hanstock, Emery, Fisher, et al., 2008; Camicioli, Moore, Kerr et al., 1999; Camicioli, Moore, Kinney, Corbridge, Glassberg & Kaye, 2003; Brück, Kurki, Kaasinen, Vahlberg & Rinne, 2004; Laakso, Partanen, Riekkinen, Lehtovirta, Helkala & Halikainen, et al., 1996).

Similarly imaging has led to significant insights into the mood disorders reported in PD. Studies using PET and SPECT techniques have provided evidence of significantly reduced neural metabolism in medicated and unmedicated PD patients with depression, compared to patients without depression and healthy controls, specifically in the frontal lobe, striatum, thalamus, amygdala, hippocampus, anterior cingulate and insula (Ceravolo, Frosini & Poletti, 2013; Huang, Ravdin & Nirenberg, 2013). Whilst no structural changes in the caudate or the putamen have been reported in relation to anxiety (Tinaz, Courtney & Stern, 2011), evidence has shown that the severity of anxiety is associated with atrophy and dopamine density in the amygdala (Vriend, Boedhoe, Rutten, Berendse, van der Werf & van der Heuvel, 2015; Remy, Doder, Lees, Turjanski & Brooks, 2005). An inverse correlation between apathy severity and cerebral metabolism in the prefrontal, temporal, parietal and limbic lobes is has been frequently reported (Santangelo, Vitale, & Picillo, 2015; Robert, Le Jeune & Lozachmeur, 2014; Huang et al., 2013; Robert, Le Jeune & Lozachmeur, 2012; Le Jeune, Drapier, & Bourguignon, 2009; Remy et al., 2005), however, the opposite results have also been found (Huang et al., 2013, Le Jeune et al., 2009; Robert et al., 2012; Robert, Le Jeune, & Dondaine, 2014). The reliability and generalisability of findings from studies using imaging techniques to investigate nonmotor symptoms in PD patients, particularly mood, are often limited as participant groups are typically small and include patients with contrasting disease characteristics including, disease severity, duration of symptoms, presence of cognitive impairment, different types of medication, not only dopamine therapies, but treatments for mood disorders, such as antidepressants. (Wen, Chan, Tan & Tan, 2016). In terms of imaging of nonmotor symptoms, the focus has been on investigations into depression, suggesting the potential to use imaging techniques to inform and develop understanding of other nonmotor symptoms, specifically anxiety, apathy and memory, is not being fully utilised.

The correspondence between STN volume and dopaminergic striatal innervation has frequently reported using MRI and SPECT techniques (Isaias, Trujillo, Summers, Marotta, Mainardi, Pezzoli, Zecca, & Costa, 2016). Dopamine transporter imaging as an accurate in vivo marker of nigrostriatal dopaminergic cell degeneration (Kraemmer, Kovacs, Perju-Dumbrava, Pirker, Traub-Weidinger & Pirker, 2014). Advancing technologies and the increasing accuracy of imaging techniques will allow for the earlier detection of PD, prior to the manifestation of symptoms, to significantly increase the understanding of pathology progression and the relationship between the neuroanatomical changes and the resulting emergence of both the motor and nonmotor symptoms of PD.

1.7. Cognitive impairment in PD

Cognitive deficits in PD are commonly reported in PD (for full review, see Dirnberger & Jahanshahi, 2013; Aarsland et al 2009; Foltynie, Brayne, Robbins & Baker, 2004), ranging from mild deficits in executive functioning in early PD to Mild Cognitive Impairment (MCI) and dementia in the more severe stages. In earlier studies of recall and recognition, evidence suggests PD patients present with impairment in the recall of previously experienced information, such as facts and personal events, but have usually been found to be less impaired at recognition of recently encountered stimuli (e.g., Higginson, Wheelock, Carroll & Sigvardt, 2005; Beatty, Staton, Weir, Monson & Whitaker, 2003; Ivory, Knight, Longmore & caradoc-Davies, 1999; Gabrieli, Singh, Stebbins & Goetz, 1996; Apollonio, Grafman, Clark, Nichelli, Zeffiro & Hallet, 1994; Breen, 1993; Cooper & Sagar, 1993; Owen, James, Leigh Summers, Marsden, Quinn, Lange & Robbins, 1992; Bondi & Kaszniak, 1991; Dewick, Hanley, Davies, Playfer & Turnbull, 1991; Heindel, Salmon, Shults, Walicke & Butters, 1989; Huber, Freidenberg, Shuttleworth, Paulsen & Clapp, 1989; Sahakian, Morris, Evenden, Heald, Levy, Philpot & Robbins, 1988; Taylor, Saint-Cyr & Lang, 1997; Taylor, Saint-Cyr & Lang, 1986; Flowers, Pearce & Pearce, 1984; Lees & Smith, 1983).

1.8. Why study memory disorder in PD

Subjective memory complaints are frequently reported in a clinical setting (Hong, Lee, Sohn & Lee, 2012; Dujardin, Duhamel, Delliaux, Thomas-Anterion, Destee & Defebvre, 2010).

Understanding memory failures in PD is essential, recent evidence suggests they are a robust indicator of conversion of cognitive status to mild cognitive status (MCI) and later dementia onset (Johnson, Langford, Garnier-villarreal, Mauricio, Morris & Galvin, 2015; Lehrner, Moser, Klug Gleib, Auff, Pirer & 2014). Memory failures are also often reported as being amongst the most troubling symptoms for patients to cope with (Gulati, Forbes, Stegie, Kelly, Clough & Chaudhuri, 2004; Hely, Morris, Reid & Trafficante, 2005) and are significant predictors of Quality of Life reports in both patients and their caregivers (Barone, Antonini, Colosimo, Marconi, Morgante, Avarello et al., 2009). Therefore, investigating and developing our understanding of memory disorder in PD is of particular clinical relevance.

1.9. Dopamine replacement therapy

The primary focus of research into the effect of dopamine repletion on cognition in PD has been directed at prefrontal dependent executive functioning (for review see Bonetti & Bonucelli, 2013). Further, these studies have largely concentrated on the effects of levodopa (l-dopa) preparations; the impact of dopamine agonists on recognition memory in PD has largely been neglected. The differential effects of non-ergot derived D2 dopamine agonists are of particular interest, firstly, as they are frequently used to manage the motor symptoms of PD, in the early stages of treatment to delay starting l-dopa treatment and to prevent early motor fluctuations and dyskinesias (Deske, 2005; Jankovic, 2005). Secondly, their use is increasing with evidence associating ergot-derived agonists such as pergolide, cabergolide, bromocriptine and dihydroergocriptine with mitro heart valve damage (Andersohn & Garbe, 2009). The effect of D2 dopamine agonists is of particular interest in PD as their use – especially pramipexole - The findings from this thesis will inform and develop understanding of the origin of recall/recollection deficits in PD, as ascertaining

whether impairments are attributable to a breakdown in prefrontal dependant strategic memory processes or medial temporal lobe dysfunction, or whether a specific type of D2 agonist or PD phenotype which is characterised by memory disorder, will be essential for the potential development of effective interventions and cognitive rehabilitation programs.

1.10. Thesis aims

The twin aims of this thesis are to present a programme of work comparing the effects of 2nd generation, non-ergot derived dopamine agonist, ropinirole and pramipexole, on recognition memory, familiarity and recollection in idiopathic PD, and to inform the design of future research which aims to further investigate this topic through the implementation of randomised controlled, crossover trial methodologies. These twin aims will be achieved through a series of linked studies which are presented in the subsequent chapter of this thesis, which will also;

- i) review the literature which has explored whether familiarity and recollection are impaired or preserved in PD, including a systematic review and meta-analysis. The literature investigating the effect that dopaminergic medication has on cognitive function in PD will also be reviewed, highlighting inconsistencies and unanswered questions, for which the research presented in this thesis aims to contribute;
- ii) compare the effects of ropinirole and pramipexole on recognition memory, familiarity and recollection in two clinically matched groups of PD patients, who already take one of the agonists as part of their daily regimen;
- iii) pilot a randomized controlled, crossover design, to compare the effect of ropinirole and pramipexole in a single cohort of PD patients to inform the design of a fully powered definitive comparative trial;
- iv) explore barriers to participation in randomized controlled, clinical trials of investigation medicinal products, with PD patients and their caregivers, to help design more accessible future clinical trials.

2. Chapter 2: Recognition memory in Parkinson's disease.

2.1. Introduction to recognition memory

The dual-process signal detection (DPSD) model of recognition memory (RM) (Yonelinas, 1994) proposes that RM is underpinned by two distinct memory processes, familiarity and recollection. Familiarity is synonymous with the subjective experience of 'knowing'. It is assumed to reflect the retrieval of 'quantitative' information, in the absence of spatial, temporal, semantic or contextual detail. According to the dual process models, familiarity is described by a signal detection process, with memory strength operating on a continuum. Conversely, recollection – a form of recall - is the experience of 'remembering', and is characterized by the retrieval of 'qualitative' information. Recollection reflects a threshold process, where if the memory strength for a stimulus falls below the threshold required for retrieval, no information will be recalled (Parks & Yonelinas, 2007; Yonelinas, 2002; 1994; Jacoby; Mandler, 1980). Due to the addition of the retrieval of contextual information, recollection responses are typically found to be associated with higher confidence ratings as opposed to familiarity responses which are supported by a continuum of confidence ratings (Gardiner, 2001). According to Aggleton and Brown's (2006) neuroanatomical model familiarity and recollection processes are subserved by different neural networks. Familiarity driven recognition is subserved by perirhinal and entorhinal circuits which also extend to dorsolateral prefrontal areas, whereas recollection and free recall rely on hippocampal pathways which extend to the anterior thalamic nucleus.

2.2. Methodological considerations

Two major methodological considerations when investigating recognition memory which will now be discussed, to avoid repetition throughout this thesis.

2.2.1. Single versus dual process models of recognition memory

Debate still exists about the nature of the processes which underpin familiarity and recollection. The dual-process signal detection (DPSD) model of recognition memory (Yonelinas, 1994; for full review see Yonelinas, 2002) proposes that familiarity and recollection are stochastically independent with contrasting subserving neuroanatomical circuitry in the medial temporal lobes. Familiarity can be well described by signal detection theory, the strength of familiarity driven recognition can vary in signal strength from weak to strong. Familiarity is believed to be subserved by the perirhinal and entorhinal circuits extending to dorsolateral prefrontal areas. Recollection is described by a threshold process where item strength must reach the threshold required for successful discrimination between studied and non studied stimuli. Recollection is subserved by the hippocampus, fornix, mammillary bodies, mammillothalamic tract and the anterior nucleus of the thalamus. In contrast to DPSD model of recognition memory, the single process unequal-variance signal-detection (UVSD) model (Donaldson, 1996) proposes that familiarity and recollection are *usually* combined into a single recognition memory strength signal which operates on a continuum, whereby recollection contributes, highly confident, fast and accurate discrimination between studied and non studied stimuli. Alternatively, familiarity is associated with less confident and less accurate responses, however when familiarity strength is stronger it can provide confident and highly accurate and recognition judgements.

Support for the DPSD model of recognition memory is found in imaging studies which report different neural substrates subserving familiarity and recollection (Villberg & Rugg, 2007; Montaldi, Spencer, Robertson & Mayes, 2006). Furthermore, lesions localised to perirhinal circuitry result in selective familiarity deficits (Pergolo & Suchan, 2013; Bowles, Crupi, Mirsattari, Pigotti, Parrent, Pruessener, Yonelinas & Köhler, 2007) and medial temporal lobe damage results on selective recollection impairment (see Montaldi & Mayes, 2012; Aggleton and Brown 1999, 2006, for reviews). The double dissociation between familiarity and recollection impairments cannot be

explained by the UVSD model, consequently the DPSM will be adopted in the research presented in this thesis. Furthermore adopting this approach will bridge a gap between this current research and previous investigations into recognition memory in PD.

2.2.2. Obtaining recollection and familiarity estimates

A number of methodologies can be used to obtain estimates of familiarity and recollection. The remember/know procedure (Tulving, 1985) was designed to explore the phenomenological experience of recognition memory, and allows for the dissociation of familiarity and recollection. In a two stage yes/no recognition memory test context, recollection is synonymous with 'remembering' contextual, qualitative information about a previously studied item, whereas familiarity is synonymous with 'knowing' an item has been studied previously, without the retrieval of any contextual information from when the item was originally studied. In the Process Dissociation Procedure (PDP; Jacoby 1991), participants are presented with a list of visual stimuli, before a second list is verbally presented. In the first of two test phases which follow (inclusion), participants have to discriminate between distractor and target items regardless of mode of presentation (visual or verbally), these endorsements are underpinned by familiarity. In the preceding test condition (exclusion), participants are instructed to only respond to targets that were verbally presented. As this condition requires participants to recall the context of the original presentation modality of the target, endorsements represent a recollection response. The remember/know procedure will be adopted in the research presented in this thesis, over PDP as this procedure recollection estimates are based on participant's estimates are based on the subjects ability to identify the source context of each item (e.g. which stimulus list). However subjects could have other recollection based information available in memory, which would not necessarily help discriminate between the source list, in contrast the remember/know procedure does not exclude any recollection justifications. Consequently, the PDP underestimates recollection performance (see Yonelinas, 2002). Other procedures can be used to measure recognition memory but will not be used as they provide overall

indications of performance, such as receiver operating characteristic curves (Yonelinas & Parks, 2007) and structural equation modelling (Quamme, Yonelinas, Widaman, Kroll & Sauve, 2004) which provide *overall* indications of recognition memory performance, and not the separated contributions of familiarity and recollection. There are however, limitations to adopting the remember/know procedure. Firstly, Wais, Mickes and Wicksted (2008) claim that this procedure measures a participant confidence in their own recognition, where high confidence judgements are claimed to be recollection a low are attributed to familiarity. Secondly, which relates to the first criticism, is the dependence on the participant to understand the dissociation between familiarity and recollection and maintain that level of understanding for the duration of the task, a particularly relevant in populations where cognitive decline may be present. Migo, Mayes and Montaldi (2012) in their review, provide number of recommendations which will be adhered to in the remember/know procedure implemented in study 1 and 2 in this thesis. Namely, providing the participant with a copy of the instructions for the test which include definitions of familiarity and recollection and checking that participants are maintaining their understanding of the instructions throughout the duration of testing.

2.3. Systematic Review and Meta-analysis

To explore the profile of familiarity and recollection in PD, a systematic literature search was carried out to find research into this area and a meta-analysis of the resulting studies was conducted.

2.3.1 Search strategy

PubMed and Web of Science databases were searched for articles up to August 2016 using the following search terms “Parkinson’s Disease” OR “PD” AND “recognition memory” OR “episodic”. In addition reference lists of original articles, reviews and previous meta-analyses were examined to identify any other relevant studies. The search was limited to journal articles written in English.

Terms like “dementia”, “Alzheimer’s” and “familial” were not used as exclusion terms in case studies had attempted to conduct comparisons between contrasting clinical groups and inappropriate studies could be excluded during the later title and abstract and full version review stages. Search results were imported into reference management software, RefWorks (www.refworks.com).

2.3.2. Study selection

Studies were included in the meta-analysis if they;

- i) used a cross sectional methodology, where a cohort of non-demented PD patients are compared to a group of healthy controls, was used;
- ii) could clearly claim independent estimates of familiarity or recollection to a recognition decision;
- iii) were presented in peer reviewed journals;
- iv) were published in the English language.

Studies were excluded from the analysis if they;

- i) used paradigms assessing recognition memory where the relative, independent contributions of familiarity and recollection to a recognition judgement cannot be determined (associative recognition tasks with a high inter-item similarity, Feeling of Knowing (FoK), gist memory, meta-memory, or Tip of the Tongue (ToT) phenomena;
- ii) used an incidental or ‘surprise’ tests of recognition memory;
- iii) provided guidance to support strategic memory processes during encoding or/and retrieval phases of a recognition task;
- iv) used paradigms involving a threshold of learning required prior to recognition phase, or there are multiple presentations of the stimuli, prior to recognition test;
- v) used different paradigms to estimate familiarity and recollection estimates from the same set of data – in these instances, data from a remember/know paradigm will be

- used to limit the variation in methods used in the meta-analysis (as the majority of the studies use the remember/know paradigm);
- vi) used confidence ratings were used to determine whether a correct recognition judgement was on the basis familiarity and recollection;
- vii) did not compare PD performance to a healthy control group.

The titles and abstracts of all identified articles were screened independently (firstly by the author of this thesis and checked independently by the primary academic supervisor) to exclude studies that did not meet the eligibility criteria. Full text versions were obtained of the selected articles were obtained and further reviewed for eligibility.

2.3.3. Data extraction

The following data was then extracted from the journal articles matching the eligibility criteria: i) authors; ii) PD group sample size, iii) control sample size; iv) the criteria by which the two groups are matched; v) PD severity measured by Hoehn and Yahr (1967) stage; vi) PD severity measured by years since diagnosis; vii) if the PD group were ON-medication or OFF-medication at the time of testing; viii) dopaminergic medication taken by the PD group; ix) the data collection method/paradigm used to obtain estimates of familiarity and recollection; x) whether a significant impairment in familiarity or recollection was reported. These data are presented in Table 2 (familiarity) and Table 3 (recollection) below.

2.3.4. Results

The initial searches resulted in the identification of 922 articles, 46 of which were duplicates and excluded. Screening of the titles and abstracts lead to the exclusion of a further 838 articles. These studies were excluded because the topic of the paper was not relevant to this review, e.g., the was about another clinical population, such Alzheimer's disease, or was investigating a different

outcome to recognition, such as the recognition of emotion in PD patients, or the recognition of nonmotor symptoms in PD by primary and secondary care clinicians. Full text versions of the remaining 38 articles were obtained for further review. From the full text review, a further 30 articles were excluded (see the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram for literature search process (Figure 1).

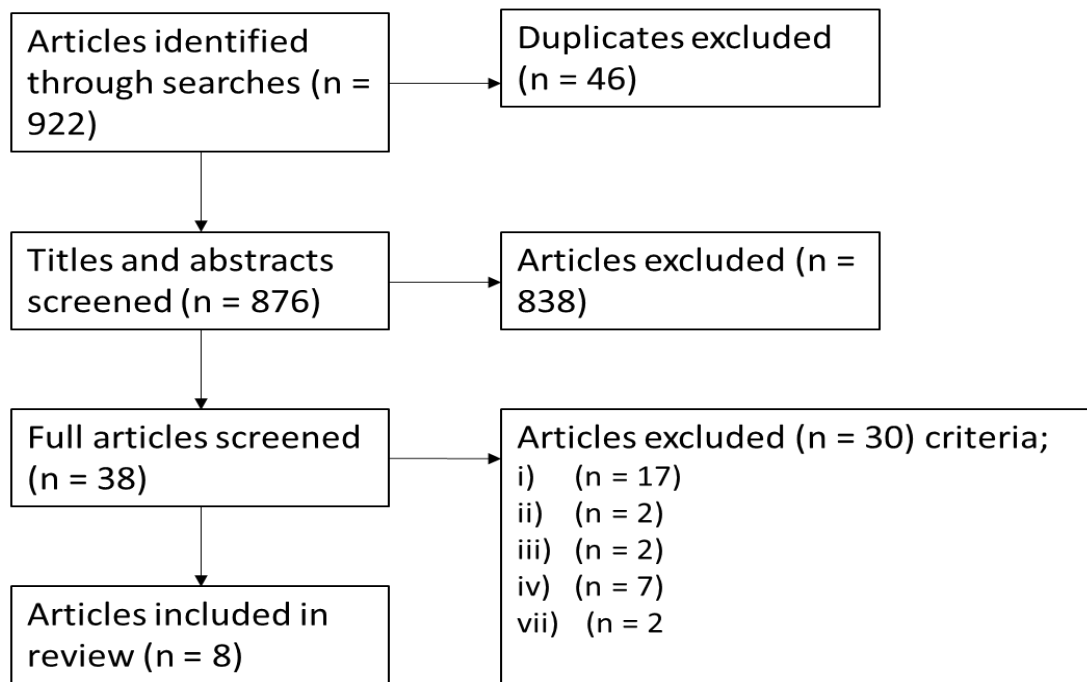


Figure 1. A PRISMA diagram of the literature search process and number of articles excluded.

Within the 8 articles meeting the eligibility criteria there were 10 independent measures of familiarity data which are presented in Table 2, and 11 independent measures of recollection which are presented in Table 3. For both familiarity and recollection, Algarabel et al (2010) has two entries to account for the inclusion of two separate PD groups mild (i) and severe (ii) and Edelstyn et al (2010) to account for two testing condition, ON-medication (i) and OFF-medication (ii). For recollection there are two data entries included from Edelstyn et al., (2015) as subjective (i) and objective recollection (ii) estimates are provided.

Table 2.

Data extracted from studies matching the eligibility criteria investigating familiarity.

Author	PD N	Control N	Matched	PD severity (HY)	PD severity (years)	Testing State	Medication	DCM	PD impaired
Davidson et al (2006)	19	23	age, education, cog function	NR	5.79 (2.46)	NR	L, DA, A, AC	RK	Yes - $p = .01$
Edelstyn et al (2007)	17	17	age, IQ, cog function	II or III	NR	ON	L, M, DA, A, AC	RK	No - p NR
Algarabel et al (2010) i	20	16	age, education, cog function	1.7	3.22 (0.3)	ON	L, M, DA	ART	No - p NR
Algarabel et al (2010) ii	19	16	age, education, cog function	2.8	10.95 (1.1)	ON	L, M, DA	ART	No - p NR
Cohn et al (2010)	9	9	age, education, cog function	NR	7.5	NR	NR	PDP	Yes - $p < .05$
Edelstyn et al (2010) i	23	21	age, education, cog function	2.61 (.69)	6.43	ON	L, M, DA	RK	No - $p = .56$
Edelstyn et al (2010) ii	-	-	-	-	-	OFF		RK	No $p = .4$
Weierman et al 2010	14	14	age, education, cog function	I,II,III	9.43	NR	Dopamine medication	RK	Yes - $p < .05$
Rodriguez et al (2014)	20	16	age, education	1.95 (0.9)	5.32 (3.0)	ON	L, DA	2AFC	No - $p = .24$
Edelstyn et al (2015)	30	22	age, IQ, cog function	2.53 (0.9)	6.31 (3.34)	ON	L, M, DA	RK	No - $p = .05$

Notes and abbreviations. A, Amantadine; AC, Anti-cholinergic; ART, Associative Recognition Task; DA, Dopamine agonist; DCM, Data Collection Method; L, Levodopa; M, Monoamine-Oxidase-B-Inhibitor; NR, Not reported; PD, Parkinson's disease; PDP, Process Dissociation Procedure; RK, Remember know paradigm.

Table 3.

Data extracted from studies matching the eligibility criteria investigating recollection.

Author	PD N	Control N	Matched	PD severity (HY)	PD severity (years)	Testing State	Medication	DCM	PD impaired
Davidson et al (2006)	19	23	age, education, cog function	NR	5.79 (2.46)	NR	L, DA, A, AC	RK	No – p NR
Edelstyn et al (2007)	17	17	age, IQ, cog function	II or III	NR	ON	L, M, DA, A, AC	RK	Yes – $p < .01$
Algarabel et al (2010) i	20	16	age, education, cog function	1.7	3.22 (0.3)	ON	L, M, DA	ART	No – p NR
Algarabel et al (2010) ii	19	16	age, education, cog function	2.8	10.95 (1.1)	ON	L, M, DA	ART	Yes – $p < .01$
Cohn et al (2010)	9	9	age, education, cog function	NR	7.5	NR	NR	PDP	No = $p = .57$
Edelstyn et al (2010) i	23	21	age, education, cog function	2.61 (.69)	6.43	ON	L, M, DA	RK	Yes – $p = .002$
Edelstyn et al (2010) ii	-	-	-	-	-	OFF		RK	Yes – $p = .01$
Weierman et al 2010	14	14	age, education, cog function	I,II,III	9.43	NR	Dopamine medication	RK	No – $p = .45$
Rodriguez et al (2014)	20	16	age, education	1.95 (0.9)	5.32 (3.0)	ON	L, DA	2AFC	Yes – $p < .05$
Edelstyn et al (2015) i	30	22	age, IQ, cog function	2.53 (0.9)	6.31 (3.34)	ON	L, M, DA	RK	Yes – $p < .001$
Edelstyn et al (2015) ii	-	-	-	-	-	-	-	-	Yes – $p = .009$

Notes and abbreviations. A, Amantadine; AC, Anti-cholinergic; ART, Associative Recognition Task; DA, Dopamine agonist; DCM, Data Collection Method; L, Levodopa; M, Monoamine-Oxidase-B-Inhibitor; NR, Not reported; PD, Parkinson's disease; PDP, Process Dissociation Procedure; RK, Remember know paradigm.

A software package (Comprehensive Meta-Analysis) was used to conduct two separate meta-analyses for familiarity and recollection. As a result of the variation of methodologies used to obtain estimates of familiarity and recollection and the heterogeneity of both data sets, as suggested significant I^2 tests (71% and 51%, respectively) a random effects model was used, consistent with the recommendation of Cuijpers (2016). Hedges g has been suggested to be more conservative than Cohen's d and Glass's delta when calculating effect sizes from studies with relatively small sample sizes and was therefore used to calculate effect sizes with 95% confidence intervals in these meta-analyses (Lakens, 2013 Cuijpers & Berking, anderssen, Quigley, Kleiboer & Dobson, 2013). Forest plots of the extracted data and the Standardised Mean Difference between PD and healthy controls are presented for familiarity and recollection data in Figure 2 below.

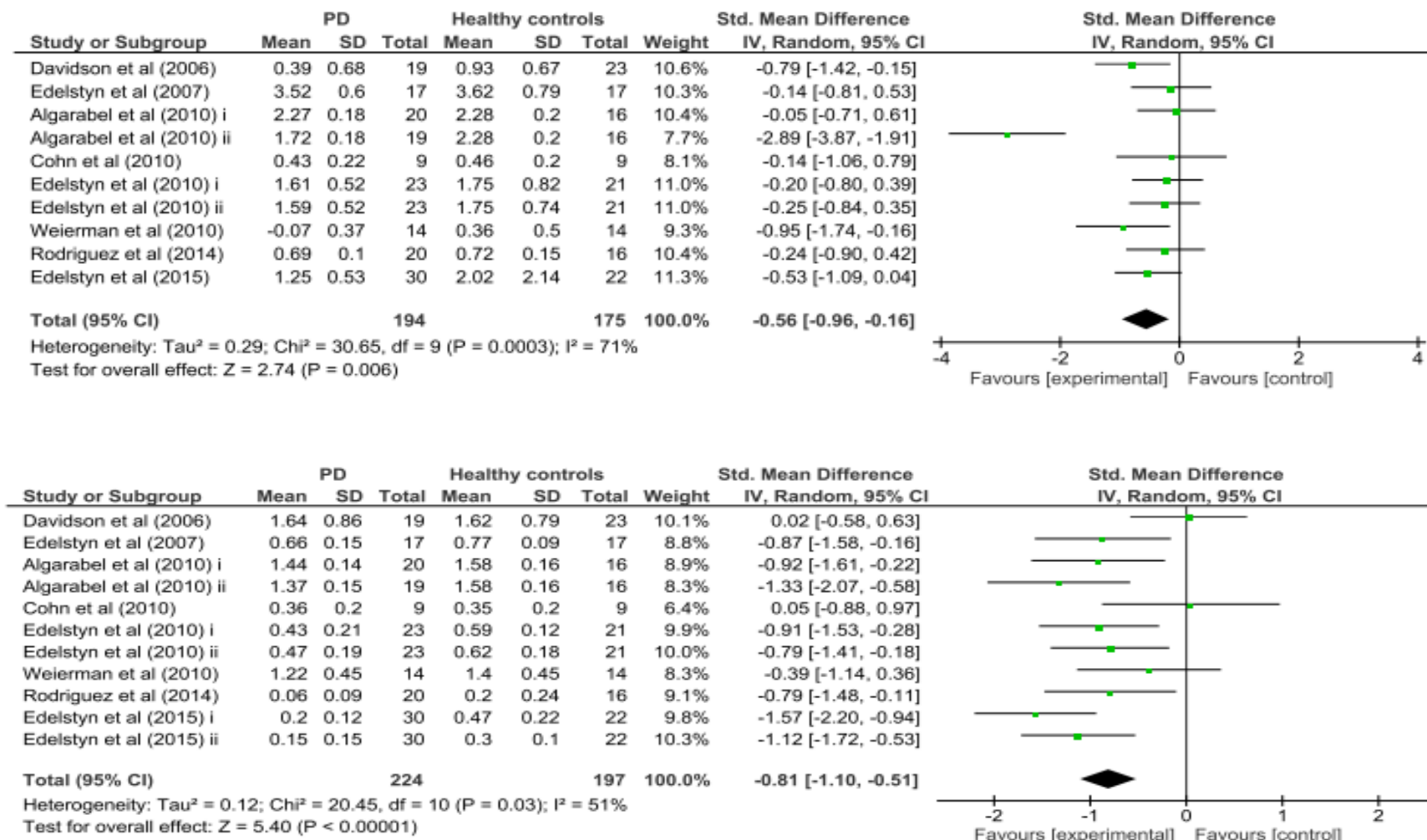


Figure 2. Forest plot and meta-analysis of the status of familiarity (upper) and recollection (lower) in Parkinson's disease compared with healthy controls.
 Notes and Abbreviations. PD, Parkinson's disease; SD, Standard deviation.

As illustrated in Figure 2, the pooled results show that familiarity is impaired in PD compared to matched healthy controls (Standardised Mean Difference (Hedge's g) = -0.56, 95% CI -0.96, -0.16, p = .006) as is recollection (Standardised Mean Difference (Hedge's g) = -0.81, 95% CI -1.10, -0.51, p < .001). Whilst the overall effects show both a familiarity and a recollection impairment, according to Cohen's (1969) interpretation of effect sizes, the familiarity deficit represents a 'medium' effect (>.50), whereas the recollection impairment is above the threshold for a 'strong' effect (>.80). Similarly, by observing the individual studies, the Standardised Mean Differences for the familiarity meta-analyses appear much more narrow and closer to the threshold for significant difference compared to recollection, which are generally much further away, suggesting a consistent but minor impairment, however, in the individual articles that were included in the familiarity meta-analysis only 30% (n = 3) report a significant familiarity impairment compared to healthy controls, whereas 63% (n = 7) of studies included in the recollection meta-analysis report a significant recollection impairment.

There are limitations of this meta-analysis, only studies published in English were used and may have biased the results, similarly, none of the studies were Randomised Controlled Trials (RCTs). A strict exclusion criteria meant only 8 studies were deemed appropriate for inclusion in the meta-analysis, resulting 10 and 11 outcome measures for effect sizes to be calculated for familiarity and recollection, respectively. Furthermore, the studies included in the meta-analysis use contrasting methodologies to obtain estimates of familiarity and recollection, which has two major implications; firstly, high levels of heterogeneity were found in both the familiarity and recollection data sets, although the use of Hedges g as a measure of Standardised Mean Difference instead of Cohen's d may have mediated the effects of this. Secondly, the findings of the individual studies are generally inconsistent with both familiarity and recollection being shown to be impaired and preserved, to examine this further, the findings of the individual studies will be the focus of discussion in the following sections.

2.4. The status of familiarity and recollection in PD

As illustrated in the systematic review, research into the status of familiarity and recollection has yielded inconsistent findings. Recollection is reported as selectively impaired in medicated PD (Edelstyn, John, Shepherd, Drakeford, Clark-Carter, Ellis and Mayes, 2015; Algarabel & Escudero 2010; Edelstyn, Shepherd, Mayes, Sherman & Ellis, 2010; Edelstyn, et al., 2007; Hay, Moscovitch & Levine, 2002), whereas familiarity is reported as preserved (Rodriguez, Escudero, Fuentes, Peset, Pitarque, Combita & Mazon, 2014). Other reports suggest a PD patients exhibit a selective familiarity deficit (Weiermann, Stephen, Kaelin-Lang and Meier, 2010; Davidson, Anaki, Saint-Cyr, Chow & Moscovitch, 2006). A double dissociation between familiarity and recollection deficits has also been reported in two separate patient groups which suggests differences in methodology used to obtain estimates of familiarity and recollection contribute to the nature of the recognition memory impairment (Cohn, Moscovitch & Davidson, 2010). Crucially, these studies report testing their patient cohorts whilst ON-medication or in an 'optimally' medicated state, which means the combined effect of PD pathology *plus* dopaminergic medication is being measured, not the relative contributions of the condition or dopamine replacement therapy on the changes in memory performance. In addition, there are a number of methodological issues which may, potentially, account for the inconsistencies of these studies which will now be discussed.

2.4.1. Methodological issues

There are number of potential reasons why the findings discussed in section 2.4. are inconsistent. The reliability and generalizability of the Cohn et al., (2010) findings are restricted by the small sample size (9 PD patients and 9 controls. Cohn et al., (2010), Weierman et al., (2010),

Davidson et al (2006) and Hay et al., (2002) use the process dissociation procedure (Jacoby, 1991) to derive estimates of recollection, whereby the correct endorsement of intact word pairs during a recognition test (that were presented as such during study), qualify as recollection, in contrast to rejecting all other forms of word pairs (new/new, old/old and rearranged old). The process dissociation procedure underestimates recollection performance for 2 main reasons. Firstly, this procedure assumes the ability to discriminate in between words pairs presented together during study and rearranged word pairs (words presented during study, but in combination with other words), is underpinned by recollection alone. However, evidence exists which shows the endorsement of words pairs can be achieved by 'unitizing' word pairs, which is supported by associative familiarity, not just recollection (Harlow, Mackenzie & Donaldson, 2010; Bastin, Van der Linden, Schnakers, Montaldi & Mayes, 2010). Secondly, as participants may have alternative recollective associated information available, for example the temporal or semantic context, which would justify a recollection response but these are not measured in this procedure (Yonelinas, 2002). This suggests that the recollection estimates in these studies are almost certainly inaccurate.

In the Cohn et al., (2010) study, the low recollection scores reported for the healthy controls in the spontaneous encoding condition are surprisingly low (mean = 0.15, the PD group's mean = 0.16) and may reflect impaired controls whose recollection performance is comparable to patients with unilateral medial temporal lobe resections tested with the same procedure (right side = 0.12, left side = 0.17)(Cohn, McAndrews & Moscovitch, 2009).

Variation in how studies have classified disease severity may also contribute to the reported inconsistencies, for example Hoehn and Yahr (1967) disease severity stages, a clinical tool used to classify PD severity based on the presentation of motor symptoms, are not always reported (Cohn et al, 2010; Davidson et al, 2006). When categorizing PD patients as either mild or moderate disease severity, the most common procedure is to allocate patients at Hoehn and Yahr (1967) stages 1-2.5 as mild and stages 3-4 as moderate (Edelstyn et al., 2010; Barnes et al., 2003; Hay et al., 2002). In the

Edelstyn et al., (2007) study, the moderate patient cohort included patients at Hoehn and Yahr (1967) stages 2 and 3. Similarly, the cohort of patients in the Weiermann et al., (2010) study is composed of patients at a variety of disease stages (9 at stage 1, 1 at stage 2.5 and 4 at stage 3).

The extent to which PD patients are medicated at the time of testing in these studies is also inconsistent. PD patients are often reported as being tested in a medicated state (Rodriguez et al 2014; Edelstyn et al., 2007; Davidson et al., 2006; Barnes et al., 2003), however they may not all be 'optimally' medicated (Hay et al 2002), or no information about whether patients were tested in a medicated state is reported (Cohn et al 2010).

2.4.2. Patient characteristics

The variability in the clinical characteristics of the PD patients in these dual process studies may contribute to inconsistencies of their respective reported findings. Firstly, the PD patients in studies by Davidson et al (2006), Cohn et al., (2010) and Weiermann et al., (2010) are reported as 'depression-free' – with no objective depression score reported. As a relationship between depression, hippocampal atrophy and episodic impairment is well established (Drakeford, 2010; Gradin & Pom, 2008; Campbell, Marriott, Nahmias, MacQueen, 2004), and it is not surprising to find recollection preserved in these three studies. Especially as Edelstyn et al., (2015) find recollection and delayed recall to be significantly negatively correlated with depression in their PD patient cohort. This also highlights the need to include depression scores in the clinical description of PD participant groups. Mood disorders like depression are particularly prevalent in PD, which may also indicate the patients included in the studies mentioned above are not generally representative of PD, but of a subset of patients who remain free of depression even at the more moderately severe stages. Furthermore, several of the investigations which report elevated depression in their PD patient cohorts also report recollection deficits (Edelstyn et al., 2015; Rodriguez et al., 2014; Edelstyn et al., 2010).

Differences in patient characteristics in these studies refer not only to changes in mood but also to the varying neuropsychological status of the PD patient groups. Executive functioning is reported as impaired in some PD patient cohorts (Rodriguez et al., 2014; Edelstyn et al., 2007; Barnes et al., 2003) but preserved in (Davidson et al., 2006) or are not assessed - or possibly just not reported - at all in others (Weiermann et al., 2012; Cohn et al., 2010; Edelstyn et al., 2010; Hay et al., 2002). Knowing the status of executive function in the PD patient cohorts in these studies is crucial, not only to assume that the participants are representative of the wider PD population (where even in mild PD executive dysfunction is often reported, but also traditionally, recall/recollection deficits in PD were assumed to be an extension of impaired executive functions which reflect the strategic memory processes required for the organization of material at encoding and retrieval (Moscovitch, 1994; Schacter, 1987). A more detailed description of this approach follows in section 2.5.1.

2.5. Origins of recollection impairment in PD

2.5.1. Prefrontal strategic memory deficit

As a result of the reduced dopaminergic activity in the frontal-striatal loop, deficits in a number of executive domains which are dependent on the integrity of the prefrontal cortex (PFC) are reported in PD (Muslimovic, Schmand, Speelman & De Haan, 2007; Foltynie et al., 2004; Bouquet, Bonnaud & Gil, 2003; See Dirnberger and Jahanshahi 2013, for full review). A meta-analysis investigating executive functioning in early, nondemented, and nonmedicated PD, suggests that verbal fluency (semantic, phonemic and alternating), working memory, inhibitory control and planning are significantly impaired in PD (Kudlicka, Clare & Hindle, 2011). Critical to each of these prefrontal dependent domains is the ability to identify, select and implement the appropriate strategies. Gershberg and Shimamura (1995) assessed two forms of strategic organization in 10 frontal lesion patients in 5 learning/recall trials for two lists of unrelated items. Strategic organization – the extent to which the same items are reported across trials, and category clustering – reporting semantically related items together. In a spontaneous condition, where patients used

their own strategies, their free recall performance was significantly impaired compared to aged matched controls, with significantly less use of strategic organization and category clustering strategies. When category clustering strategy support was provided by instructing patients to firstly state the category each word belongs to after reading the word during learning and, secondly to use categories as cues during retrieval, category clustering use was comparable to control recall scores improved although remained significantly impaired. Therefore a widely held view was that recall/recollection deficits in PD were a result of the dopaminergic dysregulation of prefrontal dependent strategic memory processes. Earlier studies provided empirical support for this proposition, for example Gabrieli and Singh (1996) reported working memory and word recall to be significantly impaired in PD patients relative to controls, and crucially that working memory performance significantly correlated with semantic clustering and relatedness and organization elements of the recall test. Bondi, Kaszniak, Bayles and Vance (1993) administered a range of executive tasks (visuoperceptual, visuoconstructive and planning) and tests of learning and memory to 19 non-dementing PD patients and 19 demographically matched healthy controls. Bondi et al., (1993) reported significant impairment in learning and memory and prefrontal dependent task performance in the PD group relative to healthy controls, however the memory deficits found in the PD patients were remediated when performance was covaried by prefrontal measures scores.

More recent evidence is inconsistent with this proposition. If it is an impaired ability to identify, select and implement organizational strategies that causes recollection impairment in PD, it is then a likely proposition that the provision of such strategies through experimental instruction during encoding and/or retrieval, should, at least in part, remediate this impairment. Edelmeyer, et al., (2015) investigated this prediction in 30 idiopathic, nondemented PD patients and 26 age and IQ matched healthy controls. Familiarity, recollection and source recall were measured using a 2 stage recognition task based on the remember/know paradigm (Tulving, 1985) under 3 separate conditions with increasing guidance and support. In a baseline condition (C1), encoding and retrieval was spontaneous and unguided, in a partial guidance condition (C2), guidance was provided during

encoding only. In a fully guided condition (C3) guidance was provided at both encoding and retrieval. In C1, recollection and source recall was significantly impaired in the PD group in relation to healthy controls, an impairment that was found consistently through C2 and C3. Whilst subjective recollection and source recall improved marginally but never significantly with the provision of strategic guidance in both the PD patients and control group with the provision of the strategic instruction but never significantly so. Familiarity was comparable across the 3 conditions. Complimentary to this evidence, in prefrontal lesion patients, such as JB (Parkin, Ward, Binschaedler, Squires & Powell, 1999), JS and BW (Rapcsak, Reminger, Glisky, Kaszniak & Comer, 1999), who present with memory impairments in yes/no recognition tasks, a liberal response bias is also reported (high hit rate and high false alarm rate), whereas a more conservative response bias is observed in PD as hit rates and false alarm rates are comparable to controls (Edelstyn et al., 2010; Edelstyn et al., 2007 & Davidson et al., 2006), which is consistent with a medial temporal lobe pathology as opposed to a prefrontal one (Rapcsak et al., 1999).

2.5.2. Medial temporal lobe pathology

The failure of the provision of guidance/strategic instruction at encoding and retrieval to remediate recollection impairment in PD suggests that the traditional prefrontal disruption explanation of episodic impairments may be inadequate, and may indicate a more amnesia-like impairment as a result of hippocampal dysfunction. Evidence of hippocampal pathology in PD has been reported previously. Braak, Tredici, Rub, de Vos, Steur and Braak (2003) examined the brains of 41 PD patients at autopsy. Whilst the disease severity and cognitive status of the patients were unknown at the time of examination, Braak et al., (2003) proposed a progressive alpha-synuclein pathology which spreads in a homogenized course beginning in structures associated with movement, dorsal motor nucleus, vagal nerves, anterior olfactory nucleus and brain stem but then progresses to the forebrain, firstly to the CA2 fields of the hippocampus and the transentorhinal regions before extending to the primary sensory and association areas and prefrontal cortex.

Anatomical evidence from structural imaging studies of PD patients suggests abnormalities in the medial temporal lobe memory systems. Camicioli, Moore, Kinney, Corbridge, Glassberg and Kaye (2003) used Magnetic Resonance Imaging (MRI) to measure hippocampal volumes of 4 age-matched participant groups; PD patients (n=10), PD with dementia (n=10), Alzheimer's Disease (AD, n=11) and healthy controls (n=12). Camicioli et al., (2003) report significantly smaller hippocampal volumes in the PD without dementia compared to healthy controls, but the severity of the atrophy was not as severe as that of the PD group with dementia or the AD group. Similarly Ibarretxe-Bilbao, Ramirez-Ruiz, Tolosa, Marti, Valldeoriola, Bargello and Junque (2008) report significant hippocampal atrophy in PD without dementia and that this grey matter loss correlated with immediate and delayed verbal recall scores. Furthermore, Ibarretxe-Bilbao et al., (2008) localise the grey matter loss specifically to the head of the hippocampus, whereas in PD patients with dementia and PD patients without dementia but with visual hallucinations – a large predictor of dementia onset in PD - atrophy involved the entire body of the hippocampus, suggesting that hippocampal pathology is present in PD without dementia, but to a different extent and nature to PD with dementia. The pattern of hippocampal atrophy in PD without dementia is not just reported in cross-sectional group studies. A longitudinal investigation by Ramirez-Ruiz, Marti, Tolosa, Bartres-Faz, Summerfield, Salgado-Pineda, Gomez-Anson and Junque (2005) measured brain atrophy through structural MRI scans and cognitive change in PD patients with and without dementia at two time points - baseline and after 25 months. To assess for change in a range of cognitive domains Ramirez-Ruiz et al., (2005) administered a range of prefrontal dependent executive tasks - working memory, block design and verbal fluency - and hippocampal dependent memory tasks - immediate and delayed verbal recall - at both time points. Ramirez-Ruiz et al., (2005) report significant reductions in hippocampal volume in both PD groups at the second time point. Whilst the verbal recall scores declined between time points they did not reach significance for the PD group without dementia, when recall scores were used as covariates the differences in hippocampal volumes between time points lost significance.

Importantly the pattern of grey matter loss in Ramirez-Ruiz et al's PD group without dementia is consistent with the neuropathological staging reported by Braak et al., (2003) in that degeneration in the limbic and paralimbic areas (stage 4) occurs before pathology spreads to the neocortical areas (stage 5 and 6). These imaging studies provide evidence of hippocampal atrophy in PD without a dementia diagnosis and provide a potential alternative explanation which may account for the recall/recollection impairment in PD. However a number of studies have failed to detect any hippocampus structural changes in nondemented PD (Beyer et al., 2009; Dashtipour et al., 2009; Jokinen et al., 2009; Bouchard et al., 2008; Burton et al., 2004; see Calabresi, Castrioto, Di Filippo & Picconi, 2013, for full review). Whilst differences in the methods of morphological assessment, patient inclusion criteria and disease durations in the patient groups may contribute to these inconsistencies, a possible role for hippocampal pathology in memory disorder in PD is still suggested. Furthermore, it is not just structural abnormalities that may be present in PD, functional changes are also possible as a result of the reduced dopaminergic innervation the hippocampus receives from dopaminergic neurons in the midbrain specifically the ventral tegmental area (VTA), which are reduced in PD as a result of disease neuropathology.

2.5.3. Hippocampus-VTA loop

It is well established that dopamine plays a critical role in long term potentiation, a form of synaptic plasticity thought to support memory encoding in the hippocampus, specifically at the CA1 region (Bliss & Colleridge, 1993). Rodent studies exploring the excitatory synaptic transmission between CA1 neurons provide evidence of a decrease in early and late phase, long term potentiation by selective antagonists which block d1 and d5 subreceptor activity (Otmakhova & Lisman, 1996). Similarly in d1 receptor knockout mice, long term potentiation is significantly reduced compared to wild type controls (Granado, Ortix, Suarez, Martin, Cena, Solis & Moratalla, 2008). Conversely increasing hippocampal dopamine content improves memory retention even in aged rats (Bernabeu,

Bevilaqua, Ardenghi, Bromberg, Schmitz, Bianchn et al., 1997; Bach, Barad, Son, Zhou, Lu, et al., 1999).

The hippocampus receives dopamine input from the VTA and form a functional loop (see Figure 3), which supports the detection of novel or salient information and uses these novelty signals to control the entry of behaviourally relevant stimuli into long term memory (for full review see Lisman and Grace, 2005). The downward arc of the loop carries hippocampal novelty signals – including information about salience and goal orientation – to the VTA, which in turn stimulates novelty-dependent firing. In the upward arc, increased dopamine release in the CA1 regions of the hippocampus, increasing long term potentiation (LTP) and consequently strengthens memory encoding (Lisman and Grace, 2005). Whilst the mechanism for the structural changes reported in the hippocampus are unclear, processes which determine fluctuations in endogenous dopamine content in the hippocampus, which is innervated by dopaminergic neurons in the midbrain, which are known to be reduced in PD as a result of disease pathology, are of critical importance to our understanding of memory disorder in PD.

an age-dependent decline in the dopamine neurons in the SNPC/MTA has been shown previously (Fearnley & Lees, 1991). Participants were administered an fMRI encoding task under two different conditions, once after L-dopa ingestion and on a second occasion after a placebo. At encoding, during fMRI participants viewed indoor and outdoor scenes - half of which were associated with reward to control for endogenous dopamine release, half remained neutral. Recall was tested at two time points, after 2 hours (short delay) and again after 6 hours (long delay). Chowdhury et al., (2012) report significantly higher delayed recall of neutral scenes after dopamine treatment in comparison to the placebo and that this effect is consistent with a narrow dose-dependent inverted 'U-shape' pattern – where an L-dopa dose of 2mg/kg of bodyweight improved recall whereas higher and lower doses had no effect, consistent with the Gotham et al., (1986) 'dopamine overdose hypothesis'. Importantly, the fMRI data confirm that this improvement in recall cannot be explained by differences in hippocampal activation during encoding, supporting a dopamine modulated, post-encoding slow consolidation process in the hippocampus. The potential for PD to show increased forgetting by virtue of additional disruption of slow consolidation remains unaddressed.

2.6. Dopamine overdose hypothesis in PD

In early PD, striatal dopamine loss is more severe in the putamen and dorsal caudate (motor and dorsolateral circuits), whilst dopaminergic content in the ventral striatum is relatively spared suggesting functions subserved by limbic and orbitofrontal circuitry, should be intact. The dopamine overdose hypothesis (Gotham, Brown & Marsden, 1986) suggests that the administration of dopaminergic medication to PD patients to remediate motor symptoms, may replete more severely depleted dopamine circuits, whilst overdosing more relatively intact ones. For example the extent of dopamine depletion in the dorsal frontostriatal circuit is more severe compared to the ventral frontostriatal circuit where dopamine levels are relatively normal in PD. L-dopa administration delivers the same dopaminergic content to both circuits, which remediates dopaminergic levels in

the frontostriatal circuit, improving working memory and task switching performance in PD, but the overdosing of the ventral frontostriatal circuit leads to the increasing impulsivity and impaired reversal learning (Poletti & Bonucelli, 2013). The relationship between dopaminergic neuronal activity and dopaminergic modulation reflects an inverted U-shape, where cognitive functions improve as dopamine levels approach the centre of the curve, but decline with deviation away from optimum levels.

2.6.1. Dopamine replacement therapy and cognition in PD

The dopamine overdose hypothesis (Gotham et al, 1986) is supported by a range of studies that have primarily focused on the effect remediation of depleted dopamine levels on executive functions, with L-dopa treatment, which has been shown to improve working memory (Cools, Myakawa, Sheridan & D'Esposito, 2010; Floel, Garraux, Xu, Breitenstein, Knecht, Herscovitch & Cohen, 2008; Mollion, Ventre-dominey, Dominey & Brousselle, 2003; Cools, Kulisevsky, Avila, Barbanoj, Antonijan, Berthier and Gironell, 1996), task switching (Cools, Barker, Sahakian & Robbins, 2003; Cools, Barker, Sahakian & Robbins 2001; Hayes, Davidson & Keele, 1998) verbal learning (Mattis, Tang, Ma & Eidelberg, 2011) planning (Hanna-Pladdy & Heilman, 2010; Cools, Stefanova, Barker, Robbins & Owen, 2002b) and attention (Fera, Nicoletti, Cerasa, Romeo, Gallo & Gioi, 2007) compared to performance after l-dopa withdrawal. Conversely, l-dopa also has the propensity to impair PD patients probabilistic reversal learning (Jahanshahi, Wilkinson, Gahir, Dharmarinda & Lagnado, 2010; Cools et al., 2001), decision making (Osman, Ryterska, Karimi, Tu, Obeso, Spekenbrink & Jahanshahi, 2014) impulsivity (Cools et al., 2003) and distractor resistance (Cools et al., 2010). More recently Miah, Olde, Dubbelink, Stoffers, Deijen, and Berendse (2012) tested the dopamine hypothesis more directly, reporting that strategy use on a spatial span working memory task is significantly impaired in *de novo* PD compared to medicated patients. For the medicated patients poorer pattern recognition memory performance was associated with patients with higher dopaminergic medication doses. These findings are consistent with the dopamine

overdose hypothesis suggesting that dopaminergic medication can improve prefrontal dependent functions subserved by circuitry where depletion is apparent, but is associated with impaired performance on tasks mediated by the medial temporal lobes where depletion is less severe in early PD.

2.6.2. Dopaminergic medication and recognition memory in PD

The majority of investigations into the effects of dopaminergic remediation on cognitive functions in PD have focused on the effect of prefrontal dependent executive functions, and comparatively few studies have explored their influence on other cognitive functions, such as recognition memory (Poletti & Bonuccelli, 2013). Significantly impaired long term potentiation (LTP) in the CA1 regions of the hippocampus and correlated memory deficits are reported in neurotoxic and genetic rodent models of PD. However, repletion of dopamine levels through l-dopa administration improves functioning to normal levels found in wild-type controls. Furthermore this effect is blocked by d1/d5 receptor antagonists, and mimicked by d1/d5 but importantly, not d2/d3 agonists (Costa, Sgobio, Siliquini, Tozzi, Tantucci, Ghiglieri et al., 2012). Very few studies have investigated the effects of dopamine medication on recognition memory in human PD patients. Edelstyn, Shepherd, Mayes, Sherman & Ellis (2010) explored the effect of dopaminergic medication on recognition memory in PD. Twelve mild (mean Hoehn and Yahr 2.1) and 11 moderate (mean Hoehn and Yahr, 3.2) PD patients completed matched versions of a recognition memory test in a medicated (ON-medication) and unmedicated (OFF-medication) condition – 21 age and IQ matched healthy controls also completed both tests in the absence of any treatment. Edelstyn et al., (2010) reported that ON-medication, recollection was significantly impaired in the moderate PD patients, compared to the mild patients and healthy controls. However, when unmedicated, recollection significantly improved in moderate PD, and was only significantly impaired in comparison to the controls. Recollection was preserved in mild PD and unaffected by medication. Familiarity was preserved in both PD groups when ON- and OFF-medication.

2.7. Complexities

2.7.1. Limitations of the dopamine overdose hypothesis

Whilst the dopamine overdose hypothesis (Gotham et al., 1986) provides a theoretical framework for investigating how medication may affect memory in PD, there are a number of limitations. Firstly, the findings from Edelstyn et al., (2010) are discordant with what the overdose hypothesis would predict. According to the overdose model, in mild PD where dopamine depletion would be less severe, relatively preserved familiarity and recollection would be expected when OFF-medication, but when ON-medication, medication induced impairments would be expected, through overdosing effects. In moderate PD, recollection impairment would be expected when OFF-medication as dopamine depletion is more severe, this impairment would therefore be remediated through dopaminergic treatment. However, the opposite findings are reported in that dopamine treatment did not overdose and impair preserved familiarity and recollection in medicated mild PD. And medication failed to remediate recollection impairments in moderate PD and actually caused further, significant impairment (Edelstyn et al., 2010). The PD patients in the Edelstyn et al., (2010) study were not just medicated with L-dopa preparations but also with dopamine agonists (ropinirole, pramipexole, rotigotine), Monoamine Oxidase B Inhibitors (selegiline, rasagiline) and Catechol-O-Methyl Transferase (COMT) inhibitors (entacapone, tolcapone). However evidence from the animal literature suggests the medicated recollection impairment is unlikely to be attributable to MAO-B inhibitors or COMT inhibitors, as selegiline and tolcapone have both been shown to not impair memory in rodents (Martins, de Lima, Laranja, Caldana, Graziotin, & Garcia, 2005; Liljequist, Haapalinna, Ahlander, Li & Mannisto, 1997). The majority of support for the dopamine overdose hypothesis and more generally, investigations into the cognitive effects of dopaminergic medication have used L-dopa which provides phasic stimulation which means the impact of dopamine agonists, which provide tonic stimulation have generally been under researched. Studies that have compared the differential effects of dopamine agonists and L-dopa have yielded interesting findings. Cools et

al., (2006) reported significant reversal learning impairments in a PD cohort medicated with pramipexole in comparison to a clinically matched PD group medicated with l-dopa only. In the same group of PD patients Brusa et al., (2003) report increases in verbal fluency and resistance to interference when medicated with l-dopa, and verbal recall, attention and set shifting impairments when medicated with pramipexole, in comparison to the cohort's own baseline OFF-medication performance. However, the effect of dopamine agonists on recognition memory has so far been under explored.

2.7.2. Timing of drug administration and patient testing

According to Chowdhury et al., (2012) any medication effects on the dopaminergic modulation of hippocampal episodic processes in PD, would only be evident 6 hours after encoding. However, recognition memory test phases have been done within 1 hour of the initial study/learning of the memoranda. Dopaminergic changes in prefrontal dependent executive functions, which reflect strategic memory processes, can be much more immediate (Miah et al., 2012; Cools et al., 2009; Brusa 2003) suggesting a dopaminergic dysregulation of prefrontal dependent strategic memory explanation of recollection impairment in PD. However this proposition is difficult to reconcile with a number of key findings from the literature. Firstly, the failure to remediate recollection impairment, with the provision of strategic instruction at encoding and/or retrieval (Edelstyn et al., 2015), is more consistent with a hippocampal dependent, amnesia-like recollection deficit. Secondly, if executive functions reflect strategic memory processes, if recollection impairments in PD are attributable to a strategic memory deficit, correlations between recollection/recall and executive functions would be reported much more consistently within the PD literature (Edelstyn et al., 2007).

2.7.3. A potential mechanism for hippocampal based memory impairment in PD

Whilst mechanisms which precipitate structural changes in the hippocampus in PD are unclear, the literature reviewed here suggests that memory impairment reported in medicated PD is not simply a result of overdosing the hippocampal-VTA model described by Lisman and Grace (2005). There is a growing body of evidence from neuroimaging research with healthy controls and rodent studies which implicate a critical role for the dopamine D2 subreceptor family in hippocampal dependent episodic processes. Takahashi, Kato, Takano, Arakawa, Okumura, Otsuka, Kodaka, Hayashi, Okubo, Ito and Suhara (2008) used Positron Emission Tomography (PET) to measure D1 and D2 receptor activity in the prefrontal cortex and hippocampus in healthy subjects (N=23) during tasks of cognitive flexibility, working memory, a verbal fluency test and measures of immediate and delayed verbal memory (Rey Osterrieth's Complex Figure Test, ROCFT; Rey's Auditory Verbal Learning Test, RAVLT). Takahashi et al., (2008) reported an inverted U-shaped relationship between cognitive flexibility and prefrontal D1 receptor binding, whilst prefrontal D2 receptor binding failed to correlate with executive or memory measures. Alternatively hippocampal D2 receptor binding showed a significant positive linear relationship with both immediate and delayed recall. Hippocampal D1 receptor binding showed no association between any executive or memory tasks. Complimentary evidence from Alzheimer's Disease patients has shown that hippocampal d2 and d3 subreceptor activity significantly positively correlates with verbal memory (Kemppainen, Laire, Laakso, Kaasinaan, Nagren, Vahlberg, Kurki & Rinne, 2003).

There is already substantial evidence that hippocampal d3 subreceptor activation contributes significantly to memory processes (Laszy, Laszlovszky & Gyertyan, 2005). Activation of d3 subreceptors inhibits the production of adenylate cyclase and mitogen-activated protein kinase which regulates cellular gene expression of cAMP-responsive element binding protein (CREB) (Yan, Feng, Fienberg & Greengard, 1999). A loss of CREB-dependent signalling in the rodent hippocampus has been associated with spatial memory impairment (Brightwell, Gallagher & Colombo, 2004) and

the somatic gene transfer of CREB has been found to alleviate memory impairments in aged rats (Mouravlev, Dunning, Young & During, 2006). Rodent studies that have manipulated d3 subreceptor activation have provided further evidence which is complimentary to the findings presented above. Xing, Meng, Wei and Li (2010) manipulated CREB production in a group of mutant mice with no d3 subreceptor expression and compared their performance on the Morris water maze task with a group of aged matched wild-type mice. The mutant mice exhibited a significantly improved performance compared to the controls on both the spatial learning and preceding memory test. Furthermore, the hippocampal CREB levels were significantly greater in the d3 subreceptor knockout mutant mice compared to the wild-type controls – no difference in CREB expression was found in prefrontal areas. Similarly, d3 subreceptor antagonist nafadotride has been shown to reduce scopolamine induced amnesia in rats (Sigala, Missale & Spano, 1997). Conversely, selective d3 subreceptor agonists induce amnesia in rats, an effect which is not be mediated by subsequent administration of d1 or d2 subreceptor antagonists (Ukai, Tanaka & Kameyama, 1997).

These findings are particularly relevant to PD as they suggest that the manipulation of D2 dopamine subreceptor activation through different dopamine agonist binding affinities may differentially impact upon hippocampal dependent episodic processes. For example, pramipexole, binds almost exclusively to d3 subreceptors and less so for d2 and d4 (Black, Hershey, Koller, Videem, Mintun, Price & Perlmutter, 2002; Piercy, 1998) whereas ropinirole has a broad affinity for d2, d3 and d4 subreceptors. Whilst this proposition has never been tested before in humans, a potential mechanism for memory impairment in medicated PD could be a result of pramipexole use, which may disrupt hippocampal dependent episodic processes by virtue of its strong binding affinity for d3 subreceptors, whereas ropinirole may not.

2.8. Structure of this thesis

Chapter 3 (study 1) describes the first empirical study of this thesis and compares the effects of pramipexole and ropinirole on recognition memory in two age, IQ and clinically matched PD

groups who are already medicated with either ropinirole *or* pramipexole as part of their daily medication regimen. The performance of these two PD groups is compared to an age and IQ matched group of Health volunteers. The discussion which follows this study highlights the importance of the findings but also the questions that remain unanswered, which in turn, provide the rationale for study 2.

Chapter 4 (study 2) is a pilot single blind, randomised controlled, crossover feasibility trial of ropinirole and pramipexole in a cohort of PD patients, on recognition memory. Data is presented to illustrate to show how the findings of study 1 can be further investigated. The relationship between recollection and immediate recall are assessed to inform if a more accessible and easier to administer measure can be used in place of a recognition memory task in a clinical setting. Furthermore recollection and immediate recall estimates are used to inform sample size calculations for a definitive trial. The feasibility of administering a range of neuropsychological tests are assessed and recruitment rates are discussed.

Chapter 5 arises out of the challenges of conducting a randomised controlled trial specifically, the barriers to recruiting patient participants to trials where patients switch medication. Consequently, study 3 is a qualitative exploration of the barriers to recruitment identified by patients who were eligible, but declined to participate in study2 (presented in chapter 4), and their caregivers.

Chapter 6 synthesises findings from the previous 3 chapters, and discusses their importance and how they contribute to the PD literature and the potential clinical implications. Furthermore, recommendations for future directions of research into memory disorder in PD and the impact that dopaminergic medication has will be suggested. This chapter also discusses other ways in which patient barriers identified in chapter 5 may be reduced in future investigation, to ensure healthy recruitment rates to clinical trials involving PD patients and other clinical populations.

3. Chapter 3: Comparing the effects of the pramipexole and ropinirole on recognition memory in two clinically matched groups with idiopathic Parkinson's disease.

N.B. Study 1 of this thesis has been published (Shepherd, T. A., Edelstyn, N. M. J., Mayes, A. R. & Ellis, S. J. (2013) Second-generation dopamine agonists and recollection impairments in Parkinson's Disease. *Journal of Neuropsychology*, 7, 284-305).

3.1. Introduction

The hallmark pathology of nondementing idiopathic Parkinson's disease (PD) is the death of dopamine-producing cells in the substantia nigra pars compacta and ventral tegmental area of the midbrain, resulting in a progressive loss of dopamine innervation in the basal ganglia (Hornykiewicz, 1966). Since a close functional relationship exists between the basal ganglia and prefrontal areas (Alexander, DeLong & Strick, 1986), it is not surprising to find evidence of PD-dependent deficits in cognitive domains that are dependent upon the integrity of the prefrontal cortex (Owen, Doyon, Dagher, Sadikot & Evans, 1998), such as working memory (Gabrieli, Singh, Stebbins, et al., 1996), planning, problem-solving (Beatty & Monson, 1990; Morris, Downes, Sahakian, et al., 1988), verbal fluency (Hanes, Andrews, Smith, et al., 1996) and response initiation (Edelstyn et al., 2007). Common to each of these domains is the requirement to select and implement appropriate strategies.

It is evidence of this kind which has led to the proposition that a PD-dependent decline in episodic memory is also contingent on a breakdown in control cognitive processes involved in the initiation and implementation of strategies required for the organization of material at encoding and retrieval (Dubois & Pillon, 1997). Consistent with this proposal, a number of PD studies have reported a significant memory impairment on tasks that require intentional organization of material at encoding (Buytenhuijs, Berger, Van Spaendonck, Horstink, Borm & Cools, 1999; Knoke, Taylor & Saint-Cyr, 1998; Taylor, Saint-Cyr, & Lang, 1990; Vingerhoet, Vermeule & Scheltens, 2005), explicit

learning of temporal order (Vriezen & Moscovitch, 1990) and associative learning (Sprengelmeyer, Canavan, Lange, & Homberg, 1995; Vriezen & Moscovitch, 1990), and visuo-spatial memory (Pillon, Ertle, Deweer, Sarazin, Agid & Dubois, 1996). As the need for organization at encoding decreases, some evidence suggests that memory deficits are reduced. For example, in Knoke et al's (1998) study, the California Verbal Learning Test was administered under 3 conditions of graded cueing to 33 patients with idiopathic PD and 42 matched normal controls. While the PD patients benefited significantly and progressively from increasingly explicit cueing, the control group did not since their performance was optimal even without cueing.

However, there is other anatomical evidence from studies of PD patients and functional brain imaging in healthy volunteers suggesting that abnormalities in the medial temporal lobe memory system may also contribute to the episodic memory impairments reported in PD. For example, hippocampal atrophy has been documented in subgroups of nondementing PD (Ibarretxe-Bilbao, Ramírez-Ruiz, Tolosa et al., 2008; Laakso, Partanen, Riekkinen et al., 1996; Camicioli, Moore, Kerr et al., 1999; Camicioli et al., 2003; Brück, Kurki, Kaasinen et al., 2004; but see Burton, McKeith, Burn et al., 2004; Bouchard, Malykhin, Martin, et al., 2008; Beyer, Apostolova, Green et al., 2009; Dashtipour, Zarifi, Hakimi et al., 2009; Jokinen, Bruck, Aalto et al., 2009); and post mortem PD studies report an accumulation of α -synuclein proteins in the CA1-3 fields of the hippocampus and the perirhinal cortex (Braak, Del Tredici, Rüb et al., 2003, see also Braak, Rüb & Del Tredici, 2006; Braak & Del Tredici, 2008). Furthermore, in healthy volunteers, event-related MRI studies have reported increased activation of the ventral tegmental area, the medial substantia nigra pars compacta and the hippocampus during explicit memory formation (Schott, Sellner, Lauer et al., 2004); with the strength of activation predicting later memory performance (Adcock, Thangavel, Whitfield-Gabrieli, et al., 2006).

So whilst there is a case to be made for the presence of medial temporal lobe abnormalities in PD, behavioural evidence of an amnesia-like memory deficit in PD is equivocal at present. Hay,

Moscovitch and Levine (2002) examined recollection memory using the process dissociation procedure in moderate PD patients and medial temporal lobe amnesic patients. Whilst both patient groups showed recollection impairments compared to a healthy control group, the magnitude of the recollection decline was much greater in the amnesic group compared to the PD patients (recollection estimates for: amnesic patients: 0.08; PD patients: 0.23; and controls: 0.35). On the other hand, a recent study by Cohn et al., (2010), which also used a process dissociation procedure to derive estimates of recollection, reported a PD recollection performance (0.16) which was comparable to a group of amnesic patients who had undergone unilateral medial temporal lobe resections (right-sided amnesic patients = 0.12; left sided amnesic patients = 0.17) reported in an earlier study (Cohn et al., 2009). Furthermore, the PD's recollection impairment in the more recent of the two studies, was *not* remediated by the provision of strategic guidance at encoding, suggesting either that the *type* of support provided was not beneficial, or that the PD patients' recollection deficit was independent of a breakdown in prefrontal cognitive control processes (Cohn, et al., 2010). Other indirect evidence of a contribution of impaired amnesia-like mnemonic processes in PD episodic memory impairment include, the low rates of correlation between recollection estimates and measures of executive function (Edelstyn et al., 2007; Drag et al., 2009); evidence of a conservative response bias on tests of yes/no recognition (i.e. low hit and false alarm rates, which is characteristic of temporal lobe lesion patients (for example, Rapcsak, Reminger, Glisky, Kaszniak & Comer, 1999) rather than the liberal response bias (high hit rates and pathologically elevated false alarm rates) which is consistent with memory impaired prefrontal-lesion patients such as patient JB (Parkin, Ward, Bindschaedler, Squires & Powell, 1999), and patients JS and BW (Rapcsak et al., 1999).

The mechanism by which functional changes in the hippocampus are mediated is uncertain, although a growing body of evidence implicates a critical role for the dopamine D2 family of receptors. In a recent imaging study of 23 male healthy subjects, Takahashi et al., (2008) measured activity at D1 and D2 dopamine receptor sites in the prefrontal cortex and the hippocampus using

positron emission tomography during executive and pure memory tasks. They reported an inverted U-shaped function between prefrontal D1 receptor binding and performance on the Wisconsin Card Sorting Test performance (see “l-dopa overdose hypothesis”, described by Gotham, Brown & Marsden, 1988; Cools, Barker, Sahakian, et al., 2001; Cools, 2006; Rowe, Hughes, Ghosh, et al., 2008), whereas prefrontal D2 binding failed to correlate to either executive or memory measures. On the other hand, hippocampal D2 receptor binding showed a positive linear correlation with both memory function and frontal lobe functions, whereas hippocampal D1 receptor binding showed no association with either memory or prefrontal functions. This is an important finding, because it suggests that in PD, different cognitive domains can each be selectively affected by drugs which differ in their respective affinities for the D2 family of subreceptors.

In a recent series of studies, we used the dual process view of recognition memory to explore dopaminergic effects on the recollection of episodic details and the assessment of familiarity during recognition (Edelstyn, et al., 2010, 2011). A widely held view is that selective hippocampal damage or dysfunction causes recollection, but not familiarity impairment (Aggleton and Brown, 1999; see also Montaldi & Mayes, 2011, for a full review), raising the possibility that hippocampal dysfunction may also be implicated in Parkinson’s disease-dependent recollection decline.

Consistent with previous studies, a dissociation was demonstrated between deficient recollection and spared familiarity in a cohort of moderately severe PD patients when tested in a medicated state. However, when the same patients were also examined following a period of medication withdrawal, whilst the same dissociation was present, the severity of the recollection decline was markedly reduced. These findings imply that dopaminergic dosing that restored dopamine concentrations in the mesostriatal pathways and ameliorated motor symptoms, at the same time overdosed the less dopaminergically depleted circuits supporting memory. However, further analyses suggested that the mechanisms underlying this medication-dependent decline were not simply associated with dopamine “overdose”, since the memory deterioration ON-medication

was only evident in a patient group medicated with l-dopa and a second generation non-ergot dopamine agonists (either pramipexole [PPX] or ropinirole [RPR]), and absent from those on l-dopa monotherapy (Edelstyn et al., 2011). As the previous study included patients medicated with PPX or RPR in the same group a direct comparison of how PPX and RPR affect recognition memory, specifically familiarity and recollection in PD has not yet been examined.

Second generation D2 dopamine agonists like PPX and RPR have a high affinity for the dopamine D₃ subreceptor, and these specific subreceptors are concentrated in the limbic areas and in particular the hippocampus (Mash, 2003). The D₃ subreceptor is part of a feedback mechanism whereby stimulation increases the synthesis and release of dopamine by the presynaptic neuron. The agonist affinity for the hippocampal D₃ subreceptor thus provides a mechanism by which recollection memory might be affected. Furthermore, subtle differences in D2 subreceptor binding profiles between PPX and RPR might lead to subtly different effects on recollection. So, for example, PPX, which binds almost exclusively to the D₃ subreceptor (Black, Hershey, Koller, Videen, Mintun, Price & Perlmuller, 2002; Piercey, 1998), might be predicted to have a more pronounced effect on recollection as compared to RPR which is characterized by a broader D2 binding profile, with a progressively lower affinity for D₃ > D₂ > D₄ subreceptors.

The aim of study 1 of this thesis is to examine the dual process view of recognition memory in separate groups of patients medicated with either PPX or RPR, and again in the same sets of patients assessed OFF-medication. Based on previous findings, a dissociation between impaired recollection and spared familiarity performance of PD patients ON- and OFF-medication is expected. Furthermore, the ON-medication decline would be most pronounced in the PPX patient subgroup where disruption of D₃ dopamine subreceptors modulating hippocampal activation would be most severe. As recollection is a form of recall, then it should be correlated to other measures of recall in PD patients. It should not, however, be correlated with measures of frontally-dependent executive functions, such as attention and working memory, if the PD recollection deficit is not caused by pre-

frontal cortex dysfunction. What should be expected if the PD recollection deficit is related to hippocampal dysfunction is not tested here, but is considered in the Discussion.

3.2. Method

3.2.1. Peer review and ethics approval

This study was subjected to independent peer review and approval was received on 7th of February 2011 (Appendix A). Ethical approval for this study was received from South Staffordshire National Research Ethics Service (NRES) Committee on 31st of May 2011 (Appendix B).

3.2.2. Participants

3.2.2.1. Patient identification and screening

PD patients were identified by searching through clinic notes from the outpatient clinic at the Department of Neurology, University Hospital of North Staffordshire. Eligible patients were contacted by telephone and if in agreement, were sent an information sheet (Appendix C). Patients opted-in to the study by returning the response form stating they were interested in taking part. Patients who had opted-in to the study were then screened by a consultant neurologist (SJE) for clinical issues or adverse events with the potential to affect performance or participation (e.g. deep brain stimulation, dopamine deregulation syndrome, fatigue, distress, medication regimen change, the recent initiation of dopaminergic treatment or the inclusion/exclusion criteria (section 3.2.2.2.)). A functional assessment of mental capacity was also completed and informed consent (Appendix D) was obtained (SJE).

3.2.2.2. Patient inclusion/exclusion criteria

Patients were eligible to participate if they conformed to the following inclusion criteria: (i) a diagnosis of idiopathic PD – determined by the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (1992); (ii) a modified Hoehn and Yahr disease severity rating of 1, 1.5, 2, 2.5, 3 or

4; (iii) Capacity to provide signed informed consent – determined by a functional assessment carried out by the clinical neurologist (Folstein et al, 1975) and a functional assessment of mental capacity; (iv) an existing medical regimen including pramipexole modified release *or* ropinirole modified release; (v) aged between 50 and 80; (vi) English as first language (vii) a Mini Mental Status Examination (MMSE, Folstein, Folstein & McHugh, 1975) minimum score of 26 to ensure homogenous levels of cognitive functioning with the group.

The following exclusion criteria were also applied: (i) familial PD; (ii) Severe PD determined by a Hoehn and Yahr (1967) disease stage rating of 5; (iii) unable to provide informed consent due to cognitive decline; (iv) another neurological illness in addition to PD; (v) a history of learning difficulty, including dyslexia; (vi) physical inability to attend screening session or to comply with treatment scheduling, such as upper limb amputations, crippling degenerative arthritis; (vii) current history of significant or uncontrollable drug abuse, alcoholism, major psychiatric phenomenology including hallucinations, lack of awareness to dyskinesias, severe dizziness or fainting upon standing, impulse control disorders, compulsive behaviours, incapacitating dyskinesias; (viii) active malignancy; (ix) immediate release preparations of ropinirole or pramipexole; (x) a medical regimen including any of the following contraindicated treatments, COMT inhibitors (entacapone/tolcapone), apomorphine, amantadine, anticholinergics, dopamine antagonists and ciprofloxacin.

3.2.2.3. Patient participants

Twenty-one patients (8 females and 13 males; mean age = 66.14, SD = 6.04) with idiopathic nondementing PD were recruited. All patients were in the mild to moderate stages of Parkinson's with a mean Hoehn and Yahr (1967) severity stage of 2.67 (SD = .67). A summary of patient recruitment is presented in Table 4. The main reason for patients not being eligible for this study was not having a current prescription of pramipexole modified release or ropinirole modified release. One patient was excluded at screening as a result of a MMSE score of less than 26.

Table 4.

Summary of eligible Parkinson's disease patients identified and recruited.

Stage of recruitment	Number of Patients
Identified as eligible.	31
Requested an information sheet.	27
Declined to participate.	5
Opted in to the study.	22
Excluded during the screening session.	1
Participated in study.	21

Patients were allocated to one of two subgroups based on their current prescription of *either* pramipexole (PPX) modified release (n = 11) *or* ropinirole (RPR) modified release (n = 10). The RPR and PPX patient groups were matched for age ($t(19), = .11, p = .91$) and a number of neuropsychological and clinical characteristics when assessed in a medicated state: current levels of functioning (Mini-Mental Status Examination, Folstein, Folstein & McHugh, 1975 [MMSE]: $t(19), = .36, p = .72$), premorbid IQ (Wechsler Test Adult Reading, Wechsler, 2001, [WTAR]: $t(19), = .64, p = .53$), depression rating (Hamilton Depression Inventory, Reynolds & Kodak, 1995, [HDI]: $t(19), = -.36, p = .72$), age of onset ($t(19), = -.57, p = .57$), illness duration ($t(19) = 1.47, p = .16$), disease severity (Hoehn and Yahr (1967) scale [HY], $t(19), = -.11, p = .92$; motor subsection of the Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987, [UPDRS]: $t(19), = .11, p = .92$) and daytime somnolence (sleepiness, Epworth Sleepiness Scale, Johns, 1991 [ESS]: $t(19), = -.27, p = .79$). Medication was also matched between the subgroups (equivalent D2 agonist dosage: $t(19), = 1.8, p = .10$, (Lyons & Pahwa, 2009); daily L-dopa dosage: $t(18), = -.003, p = .99$; monoamine-oxidase-B-inhibitor: $t(19), = .63, p = .53$; L-dopa Equivalent Daily Dose (LEDD): $t(19), = -.24, p = .83$, (Tomlinson, Stowe, Patel, Rick, Gray & Clarke, 2010).

3.2.2.4. Healthy volunteers inclusion/exclusion criteria

Healthy volunteers (HVs) were eligible to participate on the basis of the following inclusion criteria; (i) English as a first language; (ii) aged between 50 and 80 years of age; (iii) a Mini Mental Status Examination score of 26 or higher (Folstein et al, 1975). HVs were also subject to the following exclusion criteria; (i) a diagnosis of neurological or psychiatric illness (or a first degree relative with such diagnosis); (ii) major head injury (loss of consciousness for 6 hours or greater); (iii) a history of learning difficulty, including dyslexia; (iv) a history of substance abuse, including alcoholism.

3.2.2.5. Healthy volunteer group

A cohort of 10 HVs were recruited from a Healthy Volunteer panel at the School of Psychology, Keele University (participants who had taken part in studies previously and had agreed to be contacted again about future studies). The cohort consisted of 4 males and 6 females and had a mean age of 65 years (SD = 4.24).

3.2.2.6. Matching patient subgroups and healthy volunteers

The PPX and RPR subgroups were matched to the HVs for gender, age (RPR subgroup: $t(18)$, $= -.55$, $p = .59$; PPX subgroup: $t(19)$, $= -.42$, $p = .68$), premorbid IQ (WTAR, RPR subgroup: $t(18)$, $= .24$, $p = .81$; PPX subgroup: $t(19)$, $= 1.38$, $p = .18$), current levels of cognitive functioning (MMSE, RPR subgroup: $t(18)$, $= 1.28$, $p = .22$; PPX subgroup: $t(19)$, $= 1.61$, $p = .12$) but not for depression scores (HDI, RPR subgroup: $t(18)$, $= -4.60$, $p = .001$; PPX subgroup: $t(19)$, $= -3.91$, $p = .003$). All participants had normal or corrected to normal vision and were community dwelling. The demographic, neuropsychological and clinical (patients only) characteristics for the D2 agonist subgroups and HVs are summarized in Table 5.

Table 5.

The demographic, neuropsychological and clinical characteristics (patients only) of study 1 participants.

	Healthy Volunteers (n=10)	PD subgroups combined (n=21)	Ropinirole subgroup (n=10)	Pramipexole subgroup (n=11)
Parameter	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	65 (4.24)	66.14 (6.04)	66.3 (6.11)	66 (6.26)
Sex (F/M)	4/6	8/13	4/6	4/7
MMSE	29.9 (0.32)	29.36 (1.11)	29.45 (1.07)	29.27 (1.19)
HDI	2.75 (1.66)	14.42 (8.85)***	13.68 (7.32)**	16.07 (9.84)**
Premorbid IQ (WTAR)	109.9 (5.72)	107.57 (9.01)	108.9 (11.69)	106.36 (5.99)
Age of onset (years)	-	56.98 (8.06)	55.9 (8.25)	57.95 (8.15)
Illness duration (years)	-	10.21 (4.86)	11.8 (4.71)	8.77 (4.74)
Hoehn and Yahr stage				
ON-medication	-	2.67 (0.67)	2.65 (0.78)	2.68 (0.61)
OFF-medication	-	2.86 (0.59)	2.85 (0.71)	2.86 (0.50)
UPDRS				
ON-medication	-	12.76 (5.45)	12.64 (6.14)	12.7 (6.14)
OFF-medication	-	15.81 (5.11)	15.3 (3.34)	16.27 (6.45)
L-dopa dose (mg/day)	-	258.93 (236.74)	226.25 (183.75)	259 (280.69)
Equivalent Agonist dose (mg/day)	-	5.85 (5.08)	9.8 (4.85)	6.77 (2.54)
Maob-I (mg/day)	-	2.73 (3.9)	3.2 (4.07)	2.09 (3.94)
Equivalent Dopamine Load (mg/day)	-	463.46 (238.27)	450.06 (182.49)	475.64 (288.5)

Notes and abbreviations. Significant differences compared to Healthy Volunteers at, **p<.01, ***p<.001; MMSE, Mini Mental Status Examination (Folstein et al., 1975); HDI, Hamilton Depression Inventory (Reynolds et al., 1995); WTAR, Wechsler Scale of Adult Reading (Wechsler, 2001); UPDRS, Unified Parkinson's Disease Rating Scale (Fahn et al., 1987); Maob-I, Monoamine-oxidase-B-inhibitor; Equivalent Dopamine Load (Tomlinson et al., 2010); SD, standard deviation.

3.2.3. Design

A 3x2 mixed design incorporating a between groups factor, “group” (PPX vs. RPR vs. HVs) and a within groups factor, “medicated state” (ON-medication vs. OFF-medication) was used. The medicated state factor was explored by testing patient-participants in two separate testing sessions; once when they had taken their medication as usual (ON-medication) and once after a period of withdrawal (OFF-medication) to reflect 3 half-lives of ropinirole and pramipexole resulting in a 87.5% elimination of each agonist. HVs were also tested in two separate research sessions labelled “green” and “blue” to signify the absence of a treatment intervention. The “green” session was yolked to the patient’s ON-medication session and the “blue” session to the “OFF-Medication” session. The order of the ON-Medication/green and the OFF-Medication/blue testing sessions were counterbalanced across participants.

3.3.4. Stimuli

3.3.4.1. Mini Mental Status Examination

The Mini Mental Status Examination (MMSE, Appendix E) (Folstein, Folstein & McHugh, 1975) is a commonly used clinical tool used to screen for cognitive decline and dementia. This short test is comprised of 5 constructs; orientation, attention and concentration, language and praxis, construction ability and memory, and has a maximum possible score of 30. The severity of an individual’s cognitive impairment is determined by a participant’s total MMSE score. A score of less than 18 indicates severe cognitive impairment, 18-23 mild cognitive impairment whilst scores of 24-30 suggests no cognitive impairment (Folstein et al, 1975). However, Kukull, Larson, Teri, Bowen, McCormick & Pfanschmidt (1994) recommend that when screening for mild cognitive impairment, the minimum score for typical cognitive functioning should be raised to 26 to increase the MMSE’s sensitivity. In accordance with this recommendation, patients and HVs were required to achieve a minimum score of 26 to screen against mild cognitive impairment and to ensure homogenous levels of global cognitive functioning across participant groups.

3.3.4.2. The modified Hoehn and Yahr (1967) Parkinson's disease severity scale

The modified Hoehn and Yahr (1967, Appendix F) (Hoehn & Yahr, 1967) Parkinson's Disease Severity Scale is a frequently used clinical measure of the severity of Parkinson's Disease (PD). The main purpose of including this measure in the studies presented in this thesis was to ensure that patient subgroups can be matched on disease severity and to exclude patients who were at stage 5. The Hoehn and Yahr (1967) stage is determined by the criteria presented in table 6 below.

Table 6.

The modified Hoehn and Yahr (1967) staging criteria.

Hoehn and Yahr Stage	Criteria
1	Unilateral disease.
1.5	Unilateral disease plus axial involvement.
2	Bilateral disease, without impairment of balance.
2.5	Mild bilateral disease with recovery on pull test.
3	Mild to moderate bilateral disease; some postural instability; physically independent.
4	Severe disability; still able to walk or stand unassisted.
5	Wheelchair bound or bedridden unless aided.

3.3.4.3. Unified Parkinson's disease Rating Scale – motor subsection

The Unified Parkinson's Disease Rating Scale (UPDRS, Appendix G) (Fahn & Elton, 1987) is a more detailed measure of disease severity than the Hoehn and Yahr (1967) staging measure. The UPDRS motor subsection consists of 15 items relating different aspects of PD; speech, facial expression, resting tremor, action tremor of the hands, rigidity, finger taps, hand movements, alternating hand movement, leg agility, arising for a seated position, posture, gait, postural instability and bradykinesia. Each of these items is given a severity rating ranging from 0 (not a

feature of that patient) to 4 (marked or severe symptom). The scores from all 15 items are then summed to generate one overall disease severity score.

3.3.4.4. Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS, Appendix H) (Johns, 1991) is a short self-report questionnaire used to measure daytime sleepiness. Participants are presented with a number of scenarios (e.g., 'sitting and reading', 'watching TV' etc.), they are asked to rate the chance of them falling asleep in each scenario on a 4 point scale ranging from "0" (no chance of dozing) to "4" (high chance of dozing). The number ratings from each scenario are then summed to give one overall score.

3.3.4.5. Wechsler Test of Adult Reading

The Wechsler Test of Adult Reading (WTAR, Appendix I) (Wechsler, 2001) is a widely used measure of premorbid IQ. The WTAR operates on the basis of two underlying findings. Firstly, that vocabulary correlates with IQ (Crawford, Stewart, Besson, Parker & De Lacey) and that verbal skills, specifically reading ability are preserved in patients with cognitive decline (Lezak, Howieson, Loring & 2004). The WTAR consists of 50 phonetically atypical words, the pronunciation of which cannot be determined by their spelling and therefore the correct pronunciation of each word depends upon prior knowledge as opposed to current cognitive capacity. Participants are asked to read each of the 50 words aloud and errors are recorded and summed at the end. The total number of errors has a corresponding IQ estimate (the normative scores and conversion table for number of errors and associated IQ estimate can be found in the WTAR manual). The WTAR was used in the studies presented in this thesis to ensure comparable levels of intellectual functioning between patient subgroups and HVs.

3.3.4.6. Hamilton Depression Inventory

The Hamilton Depression Inventory (HDI, Appendix J) (Reynolds & Koback, 1995) is a 23-item, self-report questionnaire. Items included examine overall depression, guilt, suicide, insomnia, problems related to work, agitation, anxiety, physical symptoms and loss of weight. Each item (e.g., 'how often do you cry or feel like crying?') is accompanied by a number statements with a corresponding number (e.g., '0 – rarely', '1 – slightly more than usual', '2 - quite a bit more than usual for me', '3 – nearly all of the time'). Eleven items use multiple questions (2-4 probes) to measure specific symptoms. For example, an item measuring the psychological aspects of anxiety has two corresponding questions; one asks about the frequency of feeling anxious and the second asks about the severity of those anxious feelings.

3.3.4.7. Two stage Yes/No recognition memory test

A two stage "yes/no" recognition memory test was used to attain estimates of familiarity and recollection in both study 1 and 2. A two stage "yes/no" procedure was used to ensure that the estimates of familiarity were as reliable as possible (Eldridge, Sarfatti and Knowlton, 2002). Eldridge et al. (2002) compared the accuracy of remember and know responses when subjects were instructed to respond immediately with remember, know or old judgements and when subjects were asked to make "yes" or "no" discriminations first, before subsequently describing the "remember/know" basis of their recognition. Eldridge et al. reported that whilst "remember" responses were not affected by this manipulation, "know" responses were significantly more accurate in the two stage procedure.

Two versions of the recognition memory test were produced ("RM-Test1" and "RM-Test2") from a pool of 200 nouns, divided into 4 lists of 50 words matched for imageability (list-1, mean 5.08, SD 1.37; list-2, mean 25.07, SD 1.48; list-3, mean 5.10, SD 1.26; list-4, mean 5.08, SD 1.4), concreteness (list-1, mean 5.4, SD 1.47; list-2, mean 5.39, SD 1.45; list-3, 5.38, SD 1.46; list-4, mean 5.40, SD 1.47) and frequency (list-1, mean 62.06, SD 69.09; list-2, mean 62.76, SD 69.48; list-3, mean

61.9, SD 69.77; list-4 mean 64.4, SD 69.45, Toronto noun pool; Franklin, Hoffman & Rubin, 1982).

The four lists were then randomly assigned as either target or distractor items of RM-Test1 or RM-Test2. (The words used in the memory test are presented in Appendix K, along with piloting work showing the comparability across the different version of the test (RM-Test1 and RM-Test-2)). The order of RM-Test1 and RM-Test2 was counterbalanced across participants and ON-medication/green and OFF-medication/blue conditions.

3.3.4.8. Test of attentional performance

The auditory vigilance subtest of the Test of Attentional Performance (TAP) (Zimmerman & Fimm, 2002) was included as a measure of participant's attentional resources and cognitive control. In this task, a continuous series of alternating high (2,000 HZ) and then low (1,000 Hz) frequency sounds are played (e.g., Da-Di, Da-Di, etc.). When a variation in this sequence occurred (e.g., Di-Di or Da-Da) participants were asked to give a verbal response. Each participant experienced 20 variations in the alternating sequence over a 15 minutes period. The number of misses was used to measure of performance. Reaction times were not measured due to the motor symptoms experienced in the OFF-medication testing session. Each participant completed a 2 minute practice test before starting the full task.

3.3.4.9. Working memory

The reverse digit span task (Appendix L (Wechsler, 1997) from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997) was used as a measure of working memory and cognitive control. In this task, the experimenter reads a digit sequence (1 per second) and at the end of each sequence the participant is asked to read the digit sequence back to the experimenter in the reverse order. The task begins with sequences of two digits, which increase by one digit every two trials. The task is stopped when the participant makes two consecutive errors at any given sequence length.

3.3.4.10. Logical Memory

The logical memory (Appendix M) (Wechsler, 1997) subtest of the Wechsler Memory Scale 4th Edition (WMS-IV Wechsler, 2009) provides a measure of immediate and delayed recall (Wechsler, 1997). For the immediate recall task, participants are instructed that they will be read a short story and that they should try to remember it in as much detail as possible. Once the story has been read, the participant is asked to repeat the story back to the experimenter. This process is repeated for a second story. The delayed recall task commences after a 20 minutes period, when participants are asked to recall both stories.

3.3.5. Apparatus

A laptop with a 15" screen was used to present the recognition memory and vigilance tasks (TAP, Zimmerman & Fimm, 2002).

3.3.6. Procedure

3.3.6.1. Testing session procedure

All research sessions began at 9:00am to avoid time of day effects, and took place at the patient's home for the patient's convenience – especially during the OFF-medication session. Both the ON-medication/green and OFF-medication/blue testing sessions began with an overview of what was involved and participants were reminded that they could take breaks if necessary. For each session participants were sat at a table in front of a laptop screen. Whilst the recognition memory and vigilance tasks ran on a laptop, operation was completed by the experimenter due to the motor symptoms of the patient subgroups. Participants completed the recognition memory (the procedure for this task is detailed in section 3.3.6.2., vigilance, working memory and logical memory tasks in both the ON-medication/green and OFF-medication/blue sessions. The HDI (Reynolds et al., 1995) ESS (Johns, 1991) and WTAR (Wechsler, 2001) were only administered once so were done so in the

ON-medication/green session. Each testing session lasted approximately one hour. Once a participant had taken part in both sessions they were thanked and debriefed.

3.3.6.2. Two stage Yes/No recognition memory test procedure

The Recognition memory task was composed of two phases, a study phase and a test phase. At study, 50 target items were individually presented to participants who were asked to read each word aloud – to aid concentration – and to try to commit each word to memory for a later recognition task. Each word was presented for 3000 milliseconds followed by a 1000 millisecond inter-stimulus-interval. After a 10 minute retention interval, the 50 target items were intermixed with 50 distractor items and presented to the participant at the same rate as items in the study phase. Participants were asked to respond “yes” when they recognised a target word and “no” if they did not. A correctly identified target was labelled as a hit, whereas the incorrect endorsement of a distractor item was defined as a false alarm. Following each endorsement – irrespective of accuracy – participants made a subjective judgement about the basis of their recognition, either feelings of familiarity in the absence of recollection (e.g. a “know” response), or an explicit recollection of the item being previously presented (e.g. a “remember” response). There were no time constraints to this stage. Participants were instructed that a “remember” response could be given if the remembered: (i) where the word appeared during the study phase; (ii) the word or words that appeared just before or after the word during the study phase; (iii) personal memories, mental images, or other words – not part of the study phase – that came to mind when the word was originally presented during the study phase; (iv) thinking that the word was associated with another word presented during the study phase; (v) an emotional reaction that the word triggered when it was originally presented. “Know” responses were recorded when participants recognised a word from the study phase, but failed to remember any details associated with the word when it was presented during the study phase. Participants were familiarized with the procedure for the test phase prior to the commencement of the test and regular checks were made throughout the test

phase to ensure participants maintained a full understanding of the criteria for making the “remember/know” judgement. The recognition memory test instructions given to participants, the procedure and the criteria for justifications of either a familiarity or recollection judgement are consistent with the recommendations of Migo, Mayes and Montaldi (2012).

3.3. Results

The raw hit and false alarm means and standard deviations for recognition memory, *know* and *remember* responses for the PD group (subgroups collapsed), the PD subgroups (separated by D2 dopamine agonist, RPR or PPX) and the HVs by ON- and OFF-medication conditions are shown in Table 7. The estimates of RM (d'), familiarity (d') and recollection (pr) for the PD subgroups and the HVs are also presented in Table 1 and illustrated in Figure 4.

Table 7.

The means and standard deviations for raw hits and false alarms for recognition memory, know and remember by group and condition.

	Healthy Volunteers (n=10)		PD subgroups combined (n=21)		Ropinirole subgroup (n=10)		Pramipexole subgroup (n=11)	
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
	OFF/BUE	ON/GREEN	OFF-medication	ON-medication	OFF-medication	ON-medication	OFF-medication	ON-medication
Recognition Memory								
Hits	37.8 (5.25)	38.8 (5.12)	33.29 (7.83)	32.81 (7.19)*	33.1 (7.25)	35.9 (7.56)	31.36 (8.77)	30.54 (6.36)**
False alarms	3.4 (2.67)	3.5 (2.8)	5 (3.54)	5.52 (3.47)	5.7 (3.47)	5.4 (3.13)	4.64 (4.5)	5.64 (3.91)
<i>d'</i>	2.05 (.65)	2.10 (.62)	1.92 (.53)	1.80 (.54)	1.31 (.63)	1.35 (.52)	1.81 (.40)	1.53 (.26)
Know								
Hits	7.9 (3.45)	8.4(2.11)	9.8 (4.93)	11.67 (4.55)*	11.70 (4.67)	11.7 (4.83)	9.73 (5.83)	11.64 (4.52)
False alarms	2.1 (1.91)	2.4(2.17)	2.9 (2.79)	3.32 (2.21)	3.35 (2.21)	4.2 (2.39)	2.45 (2.84)	2.36 (1.69)
<i>d'</i>	1.31 (.63)	1.35 (.52)	1.34 (.52)	1.34 (.44)	1.31 (.63)	1.35 (.52)	1.37 (.44)	1.33 (.38)
Remember								
Hits	28.3 (6.73)	29.4 (5.76)	24 (9.17)	21.88 (8.28)*	22.15 (8.39)	25.2 (7.5)	22.45 (10.26)	18.81 (8.08)*
False alarms	1.3 (1.42)	0.9 (1.11)	2 (2.07)	2.29 (3.16)	2.35 (3.23)	1.2 (1.69)	2.18 (2.36)	3.27 (3.9)
<i>pr</i>	.55 (.13)	.52 (.15)	.47 (.17)	.41 (.17)	.54 (.13)	.52 (.15)	.40 (.17)	.30 (.11)

Notes and abbreviations. Significant within group differences (ON vs. OFF performance) at * $p < .05$, ** $p < .01$; RM, recognition memory; PD, Parkinson's disease; SD, standard deviation; *d'*, signal detection measure of discrimination accuracy; *pr*, threshold measure.

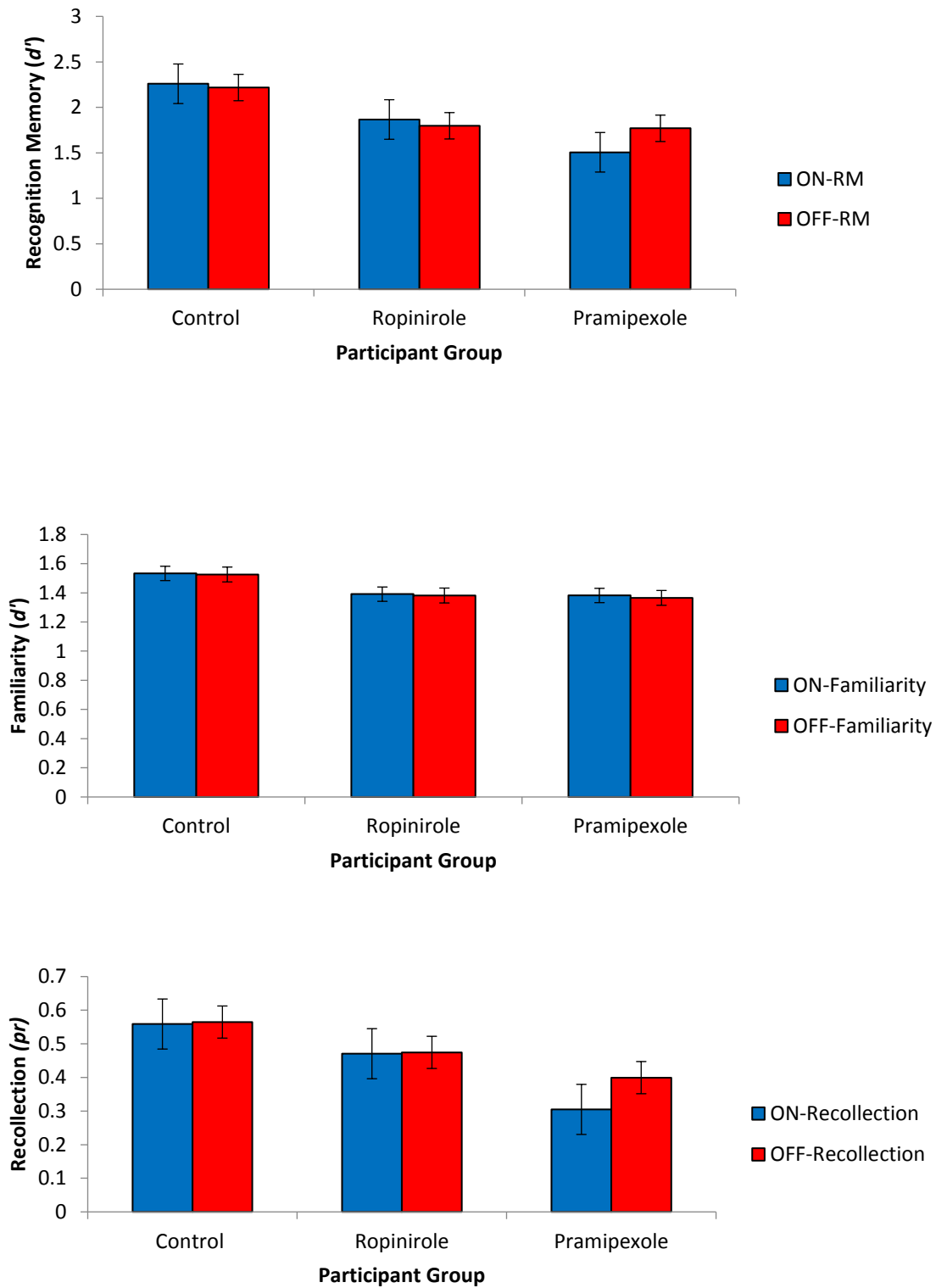


Figure 4. Estimates of recognition memory (Upper), familiarity (middle) and recollection (lower) for both ON-medication/Green and OFF-medication/Blue conditions by participant subgroup. *Notes and abbreviations.* Error bars represent the standard error of the mean. HV, Healthy Volunteers; RM, recognition memory; ON, medicated state; OFF, unmedicated state.

3.3.1. Data analysis

The distributions of depression scores of the healthy volunteer and PD groups were markedly different and the variances of the two groups were heterogeneous. However Analysis of Covariance with depression as a covariate was not run because the mean depression score which would have been applied is above the score of any of the members of the comparison group (Clarke-Carter, 2010). Homogeneity of variance within each condition was confirmed by a series of Levene's tests (ON-RM, $F = 3.11$, $p = .06$; OFF-RM, $F = .67$, $p = .52$; ON-familiarity, $F = .71$, $p = .50$; OFF-familiarity, $F = .67$, $p = .52$; ON-recollection, $F = 1.97$, $p = .16$; OFF-recollection, $F = .76$, $p = .48$). Normality of distribution across all conditions was confirmed with a series of Shapiro-Wilk tests; for the HVs, ON-RM, $p = .49$; OFF-RM, $p = .22$; ON-familiarity $p = .44$; OFF-familiarity, $p = .96$; ON-recollection, $p = .07$; OFF-recollection, $p = .72$. For the ropinirole subgroup, ON-RM, $p = .49$; OFF-RM, $p = .21$; ON-familiarity, $p = .43$; OFF-familiarity, $p = .96$; ON-recollection, $p = .07$; OFF-recollection, $p = .72$. For the pramipexole subgroup, ON-RM, $p = .68$; OFF-RM, $p = .14$; ON-familiarity, $p = .99$; OFF-familiarity, $p = .84$; ON-recollection, $p = .71$, OFF-recollection, $p = .32$. As the subgroups are relatively modest in sample size the data was also manually checked for outliers using Q-Q and box plots. No data was omitted and parametric testing of the data was conducted.

The RM (d'), familiarity (d') and recollection (pr) estimates were analysed separately using a series of 2 X 2 ANOVAs and 3 X 2 ANOVAs. In the 2 X 2 ANOVAs, the between subjects factor was Group (HV vs. PD cohort), whereas in the 3 X 2 ANOVAs the PD group was divided into subgroups based on their D2 dopamine agonist (HV vs. RPR vs. PPX). In both the 2X2 and the 3X2 ANOVA analyses, Condition (OFF-medication vs. ON-medication) remained the within-subjects factor. Significant main effects and interactions were analysed further using 1-way ANOVA, planned multiple and pair-wise comparisons, with a Bonferroni correction to control for type 1 error.

3.3.1.1. Analysis of PD subgroups combined vs HVs

Analysis of RM (d') data revealed a main effect of Group ($F(1,29) = 10.73, p = .003$), but not of Condition ($F(1,29) = .23, p = .64$), and the Interaction between Group and Condition was not significant ($F(1,29) = .1.03, p = .32$).

A second 2 x 2 ANOVA of familiarity (d') data showed no significant main effects of either Group ($F(1,29) = .33, p = .57$) or Condition ($F(1,29) = .003, p = .96$). The interaction was also not significant ($F(1,29) = .005, p = .95$). These data suggest that familiarity is spared and unaffected by Parkinson's disease or D2 dopamine agonists.

Analysis of recollection (pr) estimates revealed a significant effect of Group ($F(1,29) = 7.95, p = .009$), but not of Condition ($F(1,29) = 2.55, p = .12$), and the Interaction was not significant ($F(1,29) = 1.61, p = .22$). Taken together, these results, therefore, show a PD-dependent impairment in RM and recollection but not in familiarity, but they do not give any indication that medication state has any effect on these measures.

3.3.1.2. Analysis of PD subgroups (PPX, RPR) vs HVs

The first 3 x 2 ANOVA of RM (d') data showed a main effect of Group ($F(2,28) = 5.79, p = .008$) but not of Condition ($F(1,28) = .71, p = .41$), and the Interaction was also not significant ($F(2,28) = 2.84, p = .08$). Planned multiple comparisons revealed RM to be significantly lower in the PPX subgroup compared to the HVs ($p = .007$). There was no difference in RM between either the RPR subgroup or the HVs ($p = .07$), or between the two subgroups ($p = .62$). Further analyses with a 1-way ANOVA and planned pair-wise comparisons with a Bonferroni correction showed significant impairments in the PPX subgroup's ON-medication RM performance in comparison with the HVs ($p = .001$) but not with the RPR subgroup ($p = .10$), further no significant difference was found between the RPR subgroup and the HVs ($p = .10$). In the OFF-medication

condition no significant differences were found between the PPX subgroup and the HVs ($p=.12$) and the RPR subgroup ($p=.97$), or between the RPR subgroup and HVs ($p=.11$).

In summary, it appears that the reported decline in RM in the PD patients is dependent on the poor performance of the PPX subgroup, but this is only the case when patients are assessed in a medicated state. By contrast, RM is not impaired in patients medicated with RPR. Importantly, no differences in OFF-medication RM emerged between the subgroups, indicating that there is no difference in their baseline (unmedicated) RM performance.

The second 3x2 ANOVA of Familiarity (d') revealed no main effects of either Group ($F(2,28)$, $=.18$, $p = .83$) or Condition ($F(1,28)$, $=.006$, $p = .93$), and the Interaction was also not significant ($F(2,28)$, $= .02$, $p = .98$).

The final 3x2 ANOVA which analysed recollection (pr) data indicated main effects of Group ($F(2,28)$, $= 6.57$, $p = .005$) Condition ($F(1,28)$, $= 4.99$, $p = .03$) and the Interaction was significant ($F(2,28)$, $= 3.80$, $p = .04$). Investigation of this interaction using Bonferroni corrected planned pairwise comparisons revealed that recollection was significantly impaired in the PPX subgroup compared to the RPR subgroup ($p = .006$) and HVs ($p < .001$) when in the ON-medication condition, although no differences between RPR subgroup and the HVs emerged ($p = .13$). In the OFF-medication condition there was no significant difference between the PPX subgroup and the RPR subgroup ($p = .19$) or the HVs ($p = .09$), or, between the RPR subgroup and HVs ($p = .19$). Importantly this analysis also revealed that whilst there was no effect of Condition in the HVs ($p = .83$) or the RPR subgroup ($p = .89$), recollection in the PPX group was significantly impaired when ON- compared to OFF-medication ($p = .001$).

This profile shows a pronounced effect of PPX on recollection in PD. Patients on this drug, but not RPR, have a significant decline in recollection which is not present when the same patients are assessed following a period of medication withdrawal. Importantly, there are no differences in

the PPX subgroup's unmedicated recollection performance, indicating their baseline recollection does not significantly differ from either the HVs or the patients in the RPR subgroup.

3.3.1.3. Tests of attention, working memory, recall and somnolence

The attention, working memory and recall data were analysed using a series of 3 X 2 ANOVAs, with a between subjects factor of Group (HV vs. RPR vs. PPX) and a within subjects factor of Condition (ON-medication vs. OFF-medication). The raw data are presented in Table 8.

3.3.1.4. Attention

There were no significant effects of Group ($F(2,28) = 2.43, p = .11$) or Condition ($F(1,28) = .07, p = .79$) on attentional performance. The interaction was also not significant ($F(2,28) = .02, p = .98$).

3.3.1.5. Working memory

The effect of Group was significant ($F(2,28) = 6.8, p = .004$), whereas Condition ($F(1,28) = .00, p = .99$) and the interaction ($F(2,28) = .28, p = .76$) were not. Planned pairwise comparisons revealed that working memory was significantly impaired in the PPX subgroup compared to the HVs ($p = .001$) but not the RPR subgroup ($p = .10$). Further exploration of this effect using a 1-way ANOVA revealed a significant effect of Group in both the ON-medication ($F(2,28) = 5.05, p = .01$) and OFF-medication ($F(2,28) = 6.03, p = .007$) conditions. When ON-medication reverse digit span performance was significantly lower in the PPX subgroup compared to HVs ($p = .01$) but not the RPR subgroup ($p = .27$), an effect that was reflected in the PPX subgroup when OFF-medication ($p = .006$ and $p = .08$, respectively). No significant difference were found between the RPR subgroup and the HVs ON- or OFF-medication ($p = .28$ and $p = .54$, respectively).

3.3.1.6. Recall

Scores on the immediate and delayed recall versions of the tests were summed to produce a single recall measure reported from the ON- and OFF-medication conditions. There was significant effect of Group ($F(2,28)$, = 7.04, p = .003, but no significant effect of Condition was found ($F(1,28)$, = 1.95, p = .17), the interaction was also not significant ($F(2,28)$, = 1.63, p = .21). Planned pairwise comparisons revealed that recall was significantly impaired in the PPX subgroup compared to the HVs (p = .001) but not compared to the RPR subgroup (p = .08). The RPR subgroup and the HVs did not differ significantly (p = .07). The effect was present in both the ON-Medication and OFF-medication conditions ($F(2,28)$, = 6.96, p = .004 and ($F(2,28)$, = 4.95, p = .01, respectively). In the ON-medication condition the PPX subgroup was significantly impaired in contrast to the HVs (p = .003) but not the RPR subgroup (p = .07), this was also found in the OFF-medication condition (p = .01 and p = .06, respectively).

3.3.1.7. Somnolence

Daytime somnolence was only assessed in the ON-medication condition, and a significant group effect emerged ($F(2,28)$, = 19.31, p < .001). This reflected higher levels of sleepiness in both PPX and RPR subgroups compared to the HVs (p < .001 and p < .001, respectively), but not between the patient subgroups (p = .92).

Table 8.

The means and standard deviations for attention, somnolence, working memory and recall for each group by condition.

	Healthy Volunteers (n=10)		PD subgroups combined (n=21)		Ropinirole subgroup (n=10)		Pramipexole subgroup (n=11)	
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
	OFF/BBLUE	ON/GREEN	OFF-medication	ON-medication	OFF-medication	ON-medication	OFF-medication	ON-medication
Somnolence	-	2 (0.47)	-	11.29 (4.61)**	-	11.55 (5.18)**	-	11.7 (5.44)**
Attention	1.1 (0.74)	1 (0.67)	1.55 (1.02)	1.5 (0.87)	1.6 (1.26)	1.5 (1.08)	1.5 (.85)	1.5 (0.71)
Reverse Digit Span	9.2 (1.32)	9.4 (1.17)	7.7 (1.80)*	7.5 (2.13)*	8.4 (1.51)	8.1 (2.13)	7 (1.94)*	6.9 (2.18)*
Recall	77 (6.8)	74 (6.53)	62.25 (15.25)*	58.45 (19.03)**	63.9 (14.69)	65.2 (21.28)	60.6 (16.42)*	51.7 (14.51)**

Notes and abbreviations. Significant differences compared to Healthy Volunteers at *p<.05, **p<.01; SD, standard deviation; PD, Parkinson's disease.

3.3.1.8. Between and within-group changes in memory performance across conditions

The PD subgroup's recollection and familiarity data were transformed into z-scores (PD subgroup mean – HV Mean / Standard deviation of the HV mean) and are presented in Figure 5. Two separate 2 X 2 ANOVAs were carried out to analyse the z-score conversions of familiarity and recollection estimates, with Group (RPR vs. PPX) as the between-groups factor and Condition (ON- vs. OFF-medication) as the within-groups factor. Analysis of familiarity data revealed no significant effect of Group ($F(1,19), = .07, p = .80$) or Condition ($F(1,19), = .06, p = .81$) and the Interaction was not significant ($F(1,19), = .04, p = .85$). For recollection, an effect of Group approached significance ($F(1,19), = 3.01, p = .09$) as did Condition ($F(1,19), = 3.02, p = .09$). The interaction between Group and Condition was significant ($F(1,19), = 4.61, p = .04$). Analysis of this interaction effect using pair-wise comparisons revealed that when ON-medication recollection in the PPX subgroup were significantly impaired in contrast to the RPR subgroup ($p = .007$), however performance was comparable between both groups when OFF-medication ($p = .45$). Furthermore, whilst no significant difference emerged between the ON-/OFF-medication recollection performance in the RPR subgroup ($p = .73$), the PPX subgroup were significantly impaired ON- compared to OFF-medication ($p = .03$).

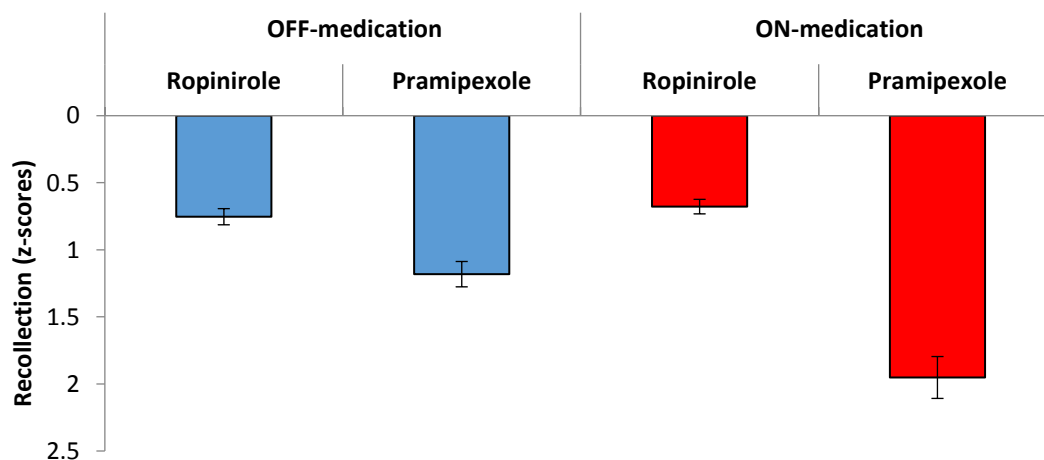


Figure 6. Z-scores of recollection estimates for both ropinirole and pramipexole PD subgroups by condition. Notes and abbreviations. Error bars represent the standard error of the mean.

3.3.1.9. Correlations between recollection and measures of recall and working memory

The PD subgroup's scores on the logical memory immediate and delayed recall subtests, working memory subtest and somnolence questionnaire were summed across both conditions and transformed into z-scores. The logical memory immediate and delayed recall z-scores were subsequently summed to yield a composite measure of recall and, alongside the standard scores for somnolence and working memory, were correlated to the z-score of the PPX subgroups' recollection performance (scores ON- and OFF-medication were also summed). The recollection performance of the PPX and the RPR subgroups, significantly correlated with the composite measure of recall ($r = .65, p = .04$ and $r = .69, p = .03$, respectively) but not to working memory ($r = -.44, p = .18$ and $r = -.24, p = .51$) or somnolence ($r = .14, p = .67$ and $r = .31, p = .38$).

3.4. Discussion

This study compared the effects of two D2 dopamine agonists (pramipexole [PPX] and ropinirole [RPR]) on recognition memory (RM), familiarity and recollection in 21 patients with nondementing mild to moderate Parkinson's disease (PD). Our predictions were derived from a variety of sources which included functional brain imaging studies of healthy volunteers reporting midbrain and hippocampal activation during encoding and retrieval (Schott et al., 2004; Adcock et al., 2006), hippocampal D₂/D₃ dopamine receptor binding during encoding tasks (Takahashi et al., 2008), post-mortem and structural imaging studies of PD showing hippocampal abnormalities (Ibarretxe-Bilbao, Ramírez-Ruiz, Tolos, et al., 2008; Laakso, Partanen, Riekkinen et al., 1996; Camicioli, Moore, Kerr et al., 1999; Camicioli, Moore, Kinney et al., 2003; Brück, Kurki, Kaasinen et al., 2004; Bouchard, Malykhin, Martin et al., 2008; Beyer, Apostolova, Green et al., 2009; Jokinen, Bruck, Aalto et al., 2009; Braak et al., 2003, Braak & Del Tredici, 2008), and the dual process theory of RM (Aggleton & Brown, 1999).

Recollection was predicted to be impaired whereas familiarity would be spared in the PD patients as has been found in previous research (Algarabel et al., 2010; Edelstyn et al., 2010; Edelstyn et al., 2007; Hay, et al., 2002), particularly under conditions that encourage adoption of a deep encoding strategy (Cohn et al., 2010). As recognition depends on both recollection (which was predicted to be impaired) and familiarity (which was predicted to be spared), no strong prediction about recognition because whether it is impaired depends on how great the contribution of recollection is to performance on a specific recognition test, and the level of this contribution is very variable. Analyses found that recognition was impaired in the patients and confirmed the prediction about recollection. When the two, differently medicated, PD subgroups were analysed together a selective recollection deficit was found that appeared not to be influenced by whether patients were ON- or OFF-medication. This finding was inconsistent with a second prediction, which is discussed next, and was shown to be illusory and misleading by further analysis.

The second prediction was that the PD patients would show more impaired recollection when on their dopaminergic agonist medication, and that this effect would be found particularly when they were medicated with PPX because of the increased affinity of PPX for dopamine D₃ subreceptors compared to RPR. These receptors are abundant in the hippocampus and we had argued that hippocampal dysfunction is found in PD and may well be at least partially responsible for patients' selectively impaired recollection. As the hippocampal dopaminergic abnormality is likely to be relatively mild, medication that optimises basal ganglia-dependent motor functions in PD may cause patients to have too much dopamine-dependent activity in the hippocampus, which will lead to selective recollection deficits. This is exactly what we found when patients were taking PPX whereas RPR had no disruptive effect on recollection, which was also unimpaired when they were OFF-medication. Not only was recollection significantly worse when patients were ON versus OFF PPX, but it was not significantly impaired in the OFF condition, although perhaps a much larger group would have shown a mild recollection deficit in this condition.

It is unlikely that the differential effect of PPX and RPR on recollection simply reflects differing PD subtypes (Selikova, Williams, Kempster, Holton, Revesz & Lees, 2009; Lewis, Foltynie, Blackwell, Robbins, Owen & Barker, 2005) for the following reasons: firstly, baseline measures of RM, recollection and familiarity were matched between the HVs and each of the PD subgroups, as well as between the subgroups in the unmedicated condition. Secondly, factorial analyses of the recollection results revealed significant main effects of Group, Condition and importantly, the Interaction ($p = .04$), which suggests that PPX causes greater decline in recollection than does RPR. However, although unlikely, this greater medication-related disruptive effect may relate to the PPX and RPR groups having differing attentional resources. These may have a direct impact on memory or be mediated indirectly through increased levels of somnolence (Ondo, Fayle, Atassi & Jankovic, 2005; Hauser, Gauger, Anderson, & Zesiewicz, 2000). But, this seems unlikely since there were no differences in daytime somnolence, attention or working memory between the PD subgroups, and somnolence and attention scores failed to correlate with recollection.

It would seem, therefore, that when PD patients have a mean HY disease stage of 2.7, their recollection deficit arises largely or wholly because of specific dopaminergic medication effects. Our earlier work indicated that patients with mild PD (HY mean of 2.1) did not show recollection deficits even when medicated with PPX and that more impaired patients (HY mean of 3.2) have impaired recollection even when in the OFF condition (Edelstyn et al., 2010). However, in the mild to moderate stage of their disease (HY mean of 2.7), most or all, of PD patients' recollection deficit is caused by specific kinds of dopaminergic medication, which we know includes PPX and may include other agents with similar modes of action.

The patients showed intact familiarity regardless of their specific medication and whether they were in the ON- or OFF-medication condition. This selective recollection deficit pattern has been associated with hippocampal dysfunction (see Montaldi & Mayes, 2010 for a discussion), although it might also be caused by frontal dysfunction because recollection is more dependent on executive control functions strategic memory processes than familiarity (Dubois & Pillon, 1997).

However, patient's recollection performance did not relate to attentional and working memory measures which are dependent on frontal function, and therefore we have no evidence that frontal dysfunction whether a result of the disease, medication or both was contributing to this recollection deficit.

This study suggests that PPX may contribute to, or possibly sometimes even cause, a recollection impairment in mild to moderate PD. One possible scenario is that initially, as the motor disease develops, and when no medication is being used, neither recollection nor familiarity is impaired. However, when patients progress to a mean HY of around 2.7 certain dopaminergic medications cause a selective recollection deficit and, as the disease progresses further (to around HY of 3.2) recollection is impaired even when patients are off medication. Whether as the disease progresses further all dopaminergic medications cease to cause further disruption or even to reduce recollection deficits (which may by this stage also be accompanied by familiarity deficits) remains to be properly investigated. Although, as the disease progresses, both medial temporal lobe and frontal lobe dysfunction that are directly caused by the disease may contribute to recollection (and possibly familiarity) impairments, and different medications may decrease, increase or have no effect on these memory-related dysfunctions, our study found no direct evidence that a disease-induced or medication-induced frontal dysfunction contributed to the selective recollection deficit we observed. It seems more likely that PD patients at a mean HY stage of 2.7 may have a mild disease-induced hippocampal dysfunction worsened by certain kinds of dopaminergic agonist medication, one of which is PPX. This is compatible with other evidence of a recollection decline in PD attributed to hippocampally-mediated processes (Cohn et al., 2010).

The proposed mechanism underlying the functional change in the hippocampal modulation of recollection processes focuses on the D2 family of dopamine receptors and more specifically D₃ subreceptors in the hippocampus and their role in memory formation (Takahashi et al., 2008). It is possible that the strong affinity of PPX for D₃ subreceptors may be disrupting the hippocampally-dependent recollection processes and *not* the strategic memory processes which are dependent on

prefrontal structures, where D₃ receptors are much less prevalent (Hurley & Jenner, 2006; Wang & Pickel, 2002; Levesque, Diaz, Pilon, Martress, Giros & Souil, 1992). This may provide explanation as to why working memory capacity, reported to reflect or even mediate strategic memory processes (Gabrieli et al., 1996; Higginson et al., 2003, respectively), was comparable in the PPX subgroup in both the ON- and OFF-medication conditions and why it failed to correlate with recollection performance, which instead, was found to only correlate with other recall measures. Whilst the evidence about the mechanism of the differential effects of RPR and PPX on recollection is indirect and rests heavily on the differences in the binding profile of PPX and RPR, other explanations may emerge.

Generally, the hippocampal regions supporting recollection processes have been shown to be vulnerable to PD pathology in both post mortem (see Braak, et al., 2003; Braak & Del Tredici, 2008) and structural neuroimaging studies (see Camicioli, Moore, Kerr et al., 1999; Camicioli, Moore, Kinney et al., 2003); however, the role that the dopaminergic modulation of these areas has on the recollection profile of PD clearly requires further investigation. For example, PET studies could assay how dopaminergic activity is modulated by different medications when patients are engaged in recollection or recall activities, and determine whether this activity is correlated with patient recollection performance levels.

In conclusion, this study demonstrated that idiopathic, nondementing mild to moderate PD (mean HY of 2.7) can cause a selective impairment of recollection whilst sparing familiarity during recognition. Furthermore the current study provides evidence – for the first time – that the use of the D2 dopamine agonist pramipexole, but not ropinirole, may induce a hippocampally-dependent selective recollection impairment in PD, which is minimal or absent when patients are effectively drug free. This study, therefore, provides preliminary support for the idea that some drugs effective in the treatment of the motor symptoms of PD can have an adverse effect on important aspects of memory at least at a certain stage of the disease. Further, the study suggests that this effect is more

likely to depend on the disruptive effects of drugs, like PPX, on hippocampally-dependent processes rather than frontal function.

4. Chapter 4: A randomised controlled, crossover pilot trial to compare the effects of pramipexole and ropinirole on recognition memory in idiopathic Parkinson's Disease without cognitive impairment.

4.1. Introduction

The main finding of study 1 (chapter 3) revealed, for the first time, that PD patients, when medicated with pramipexole present with a significant recollection impairment compared to estimates obtained after a period of withdrawal. This medication induced recollection impairment was not seen in a second group of PD patient medicated with ropinirole. Furthermore, recollection performance was comparable when both PD subgroups were tested after a period of withdrawal from their respective dopamine agonist, suggesting the findings are not attributable to a global cognitive decline. The ON-medication recollection performance of the pramipexole PD subgroup was also significantly impaired in contrast to the ropinirole PD subgroup tested ON-medication.

Several important factors need to be considered with this set of findings. Firstly, the two PD subgroups were matched on a range of demographic and disease severity characteristics so findings are not attributed to a potentially more advanced globally cognitively impaired or older group of PD patients. Secondly, the two PD subgroups were matched for dopamine therapy dosage, suggesting the pramipexole induced recollection impairment is not a simply a dopamine overdose effect. Thirdly, difference in recollection are unlikely to be a result of other putative factors, such as attention or somnolence, as these measures were comparable between the two PD subgroups, and unaffected by the ON-/OFF-medication manipulation.

A limitation of study 1 relates to the design. The between groups methodology employed in study 1 limits how the nature of the findings can be interpreted, leaving 3 potential scenarios;

- i) A phenotype effect; a phenotype, within the initial diagnosis of PD, characterized by memory impairment which is particularly vulnerable to dopaminergic medication, for which pramipexole is only a marker.

- ii) A drug effect; where pramipexole impairs recollection in PD.
- iii) A phenotype*drug interaction; A phenotype of PD, marked by a recollection impairment, which is further vulnerable to pramipexole.

4.1.1. Phenotype

It is well established that PD is a heterogeneous condition, and the subgrouping of PD patients, based on a patient's symptomology, within the initial diagnosis of PD, is a distinct possibility. However the majority of work that has attempted to subgroup patients has predominantly used the motor symptom presentation as the focus of such categorisation. In a recent systematic review of articles cited on PubMed between 1980 and 2013, Tenganalt and Jankovic (2014) used *Parkinson's Disease, Parkinsonism, tremor, postural instability and gait disturbances* as the search terms. Tenganalt and Jankovic found that the most accurate way of subgrouping PD was into two subtypes i) tremor dominant and ii) non tremor dominant characterised by postural instability and gait disturbance. Whilst this offers some indication of how PD can be subgrouped into phenotypes, it seems simplistic, and limited in its clinical usefulness to only have two groups to cover the heterogeneous nature of PD. Similarly, the omission of any of the nonmotor symptoms severely limits the generalisability of such findings, and leads to the possibility that those two groups could be subcategorised further.

Lewis et al., (2005) used statistical cluster analysis of demographic, motor, mood and cognitive assessment data from 120 early stage PD patient (Hoehn and Yahr (1967) stages 1-3) to categorise patients into the following subgroups; i) young disease onset, ii) tremor dominant, iii) non tremor dominant subgroup with significant levels of cognitive decline and mild depression, and iv) rapid onset of disease progression without cognitive impairment. This study suggests the importance of cognitive status and mood changes informing potential phenotypes of PD, however cognitive symptoms in PD can be heterogeneous like motor symptoms, and different cognitive domains could potentially differentially effects in contrasting phenotypes which are split by motor characteristics. In

an attempt to analyse the impact of the predominant motor based classifications and depression on cognition in PD, TremLAY, Achim, Macoir and Monetta (2013) conducted a meta-analysis of 27 studies from 1985-2012. TremLAY et al., calculated the average effect size of these factors on the Mini-Mental Statues Examination (MMSE, Folstein et al., 1984) as this was the most used cognitive test in those studies. Results suggested those PD participants with tremor predominant motor symptoms or those with higher levels of depression had more severe cognitive impairments. This review is limited as it can only use the MMSE to encompass something as expansive and as complex as cognitive status in PD. The MMSE itself is composed of several cognitive domains, but it is not an exhaustive measure of cognitive status. However, this study does show the importance of the inclusion of nonmotor symptoms such as depression and cognition to phenotyping work in PD despite the pathogenic mechanisms, which underlie different phenotypes of PD requiring much further investigation. The implications of which will be far reaching, especially in the clinical management of the condition, specifically if certain symptoms, such as depression or tremor are better treated by particular a PD drug.

Evidence form clinical trial literature has shown the efficacy of pramipexole over placebo in treating PD patients who present with depressive symptoms (for a review of placebo controlled trials, see Troeung, Egan & Gasser, 2013). Barone, Scarzella, Marconi, Antonini, Margante, Bracco et al., (2006) also showed from a parallel armed design, the superior effectiveness of pramipexole over sertraline in the treatment of depressive symptoms in PD. The initial criticism of the evidence showing the using pramipexole in the treatment of depressive symptoms in PD, was trying to distinguish between a direct effect on depression, or indirectly through the improving the patient's motor symptoms. However, Barone, Poewe, Albrecht, Debieuvre, Massey, Rascol et al., (2010) used a randomised controlled, double blind, placebo controlled trial of pramipexole in the treatment of depressive symptoms in 287 mild to moderately severe PD patients. Not only did Barone et al., (2010) show a hugely significant, positive treatment for the depressive symptoms, they used a

pathway, regression analysis to show that 80% of the variance of the improvement in depressive symptoms was a pure treatment effect, and not as a result of an improvement in motor symptoms.

Similar to depressive symptoms, pramipexole has also been shown to be particularly effective in the treatment of tremor in early (Herceg, Nagy, Pal, Jansky, Kesmarky, Kermoly et al., 2012), and advanced PD (Kunig, Pogarell, Moller, Delf & Oertel, 1999), and at a variety of severity stages using a randomised, double blind, placebo controlled trial (Pogarell, Gasser, van Hilten, Spieker, Pollentier, Meier et al., 2002). Furthermore its clinical effectiveness has been shown to be consistent in the treatment of resting, postural and kinetic tremor (Levik, Boiko, Nesterova, Otcheskaia, Zhuravleva, artemova et al., 2010). Evidence of this nature has impacted on the clinical management of PD, particularly in the selection of appropriate dopamine agonist selection by the consulting physician. Typically, with the higher levels of tolerability of ropinirole, unless a patient presents with a tremor dominant manifestation, or with particularly depressive symptoms, the default D2 dopamine agonist is ropinirole (See Antonini, Barone, Ceravolo, Fabbrini, Tinazzi & Abbruzzes, 2010). Accordingly, for the purposes of the trial presented in this chapter, PD patients medicated with ropinirole prior to entering the trial are labelled “RPR phenotype” and pramipexole “PPX phenotype”.

4.1.2. Drug mechanism

There is a growing body of evidence from neuroimaging research with healthy controls and rodent studies which implicate a critical role for the dopamine D2 subreceptor family in hippocampal dependent episodic processes. Takahashi, Kato, Takano, Arakawa, Okumura, Otsuka, Kodaka, Hayashi, Okubo, Ito and Suhara (2008) used Positron Emission Tomography (PET) to measure D1 and D2 receptor activity in the prefrontal cortex and hippocampus in healthy subjects (N=23) during tasks of cognitive flexibility, working memory, a verbal fluency test and measures of immediate and delayed verbal memory (Rey Osterrieth’s Complex Figure Test, ROCFT; Rey’s Auditory Verbal Learning Test, RAVLT). Takahashi et al., (2008) reported an inverted U-shaped relationship between cognitive flexibility and prefrontal D1 receptor binding, whilst prefrontal D2

receptor binding failed to correlate with executive or memory measures. Alternatively hippocampal D2 receptor binding showed a significant positive linear relationship with both immediate and delayed recall. Hippocampal D1 receptor binding showed no association between any executive or memory tasks. Complimentary evidence from Alzheimer's Disease (AD) patients has shown that hippocampal d2 and d3 subreceptor activity significantly positively correlates with verbal memory (Kemppainen, Laire, Laakso, Kaasinaan, Nagren, Vahlberg, Kurki & Rinne, 2003). These findings are particularly relevant to PD as they suggest that the manipulation of D2 dopamine subreceptor activation through contrasting dopamine agonist binding affinities may differentially impact upon hippocampal dependent episodic processes.

There is already substantial evidence that hippocampal d3 subreceptor activation contributes significantly to memory processes (Laszy, Laszlovszky & Gyertyan, 2005). Activation of d3 subreceptors inhibits the production of adenylate cyclase and mitogen-activated protein kinase which regulates cellular gene expression of cAMP-responsive element binding protein (CREB)(Yan, Feng, Fienberg & Greengard, 1999). A loss of CREB-dependent signalling in the rodent hippocampus has been associated with spatial memory impairment (Brightwell, Gallagher & Colombo, 2004) and the somatic gene transfer of CREB has been found to alleviate memory impairments in aged rats (Mouravlev, Dunning, Young & During, 2006). Rodent studies that have manipulated d3 subreceptor activation have provided further evidence which is complimentary to the findings presented above. Xing, Meng, Wei and Li (2010) manipulated CREB production in a group of mutant mice with no d3 subreceptor expression and compared their performance on the Morris water maze task with a group of aged matched wild-type mice. The mutant mice exhibited a significantly improved performance compared to the controls on both the spatial learning and preceding memory test. Furthermore, the hippocampal CREB levels were significantly greater in the d3 subreceptor knockout mutant mice compared to the wild-type controls – no difference in CREB expression was found in prefrontal areas. Similarly, d3 subreceptor antagonist nafadotride has been shown to reduce scopolamine induced amnesia in rats (Sigala, Missale & Spano, 1997). Conversely, selective d3

subreceptor agonists induce amnesia in rats, an effect which is not be mediated by subsequent administration of d1 or d2 subreceptor antagonists (Ukai, Tanaka & Kameyama, 1997).

These findings are particularly relevant to PD as they suggest that the manipulation of D2 dopamine subreceptor activation through different dopamine agonist binding affinities may differentially impact upon hippocampal dependent episodic processes. For example, pramipexole, which binds almost exclusively to d3 subreceptors and less so for d2 and d4 (Black, Hershey, Koller, Videem, Mintun, Price & Perlmutter, 2002; Piercy, 1998) whereas ropinirole has a broad affinity for d2, d3 and d4 subreceptors. Whilst this proposition has never been tested before in humans, a potential mechanism for memory impairment in medicated PD could be a result of pramipexole use, which may disrupt hippocampal dependent episodic processes by virtue of its strong binding affinity for d3 subreceptors, whereas ropinirole may not.

4.1.3. A phenotype*drug interaction

This is a synthesis of the phenotype and drug effects discussed above, whereby the PPX phenotype may have a baseline recollection impairment OFF-medication or when medicated with ropinirole, but this existing impairment is particularly vulnerable to pramipexole, which exacerbates this impairment further. In this scenario, the RPR would not exhibit a recollection impairment and performance is unaffected by either pramipexole or ropinirole.

4.1.4. A randomised controlled crossover design

To explore these 3 scenarios which arise from study 1, clearly, a crossover design trial is required, whereby a cohort of PD patients who are already taking RPR or PPX are randomly allocated to 1 of 2 treatment arms. In treatment arm 1 patients begin taking pramipexole as part of their dopaminergic medication regimen for 6 weeks, then undergo 2 separate testing sessions, once in an ON-medication condition, and a separate session after a period of withdrawal (OFF-medication), before switching to a pramipexole treatment arms and switching to pramipexole and undergoing an

ON-medication and OFF-medication session. The other half of PD patients, in treatment arm 2, begin on ropinirole before switching to pramipexole. In each session patients undergo tests of recognition memory and other clinical and executive measures, as illustrated in Figure 6. As this is a pilot trial a sample of 50 PD patients was decided upon based on the recommendations of Sim and Machin (2010). More detail on the design is given in section 4.2.3.

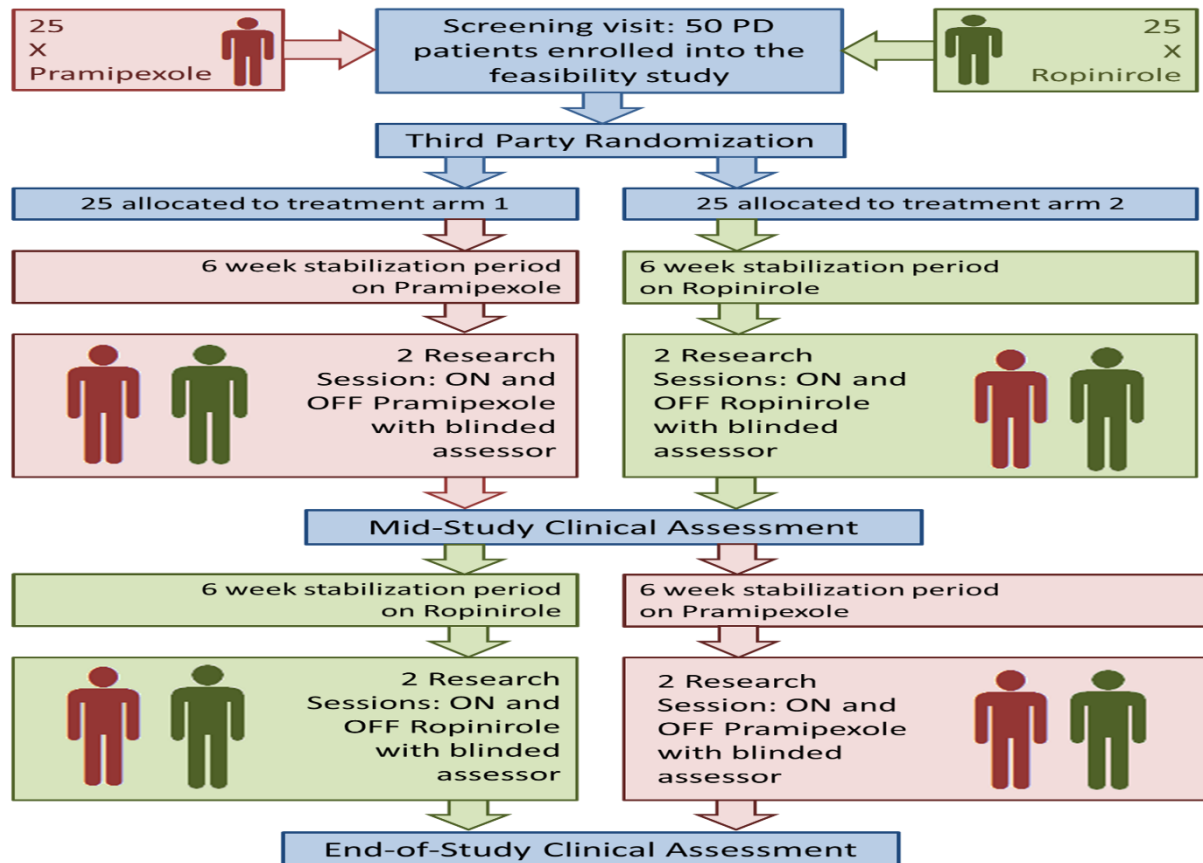


Figure 6. Schematic flow diagram of the randomised controlled, crossover design.

Implementing this design allows for the exploration of the 3 possible scenarios for the findings of study 1. If there is a PPX phenotype which is particularly vulnerable to memory impairment, especially when medicated it would be expected that that group of participants would be impaired when tested on both pramipexole and ropinirole as illustrated in Figure 7.

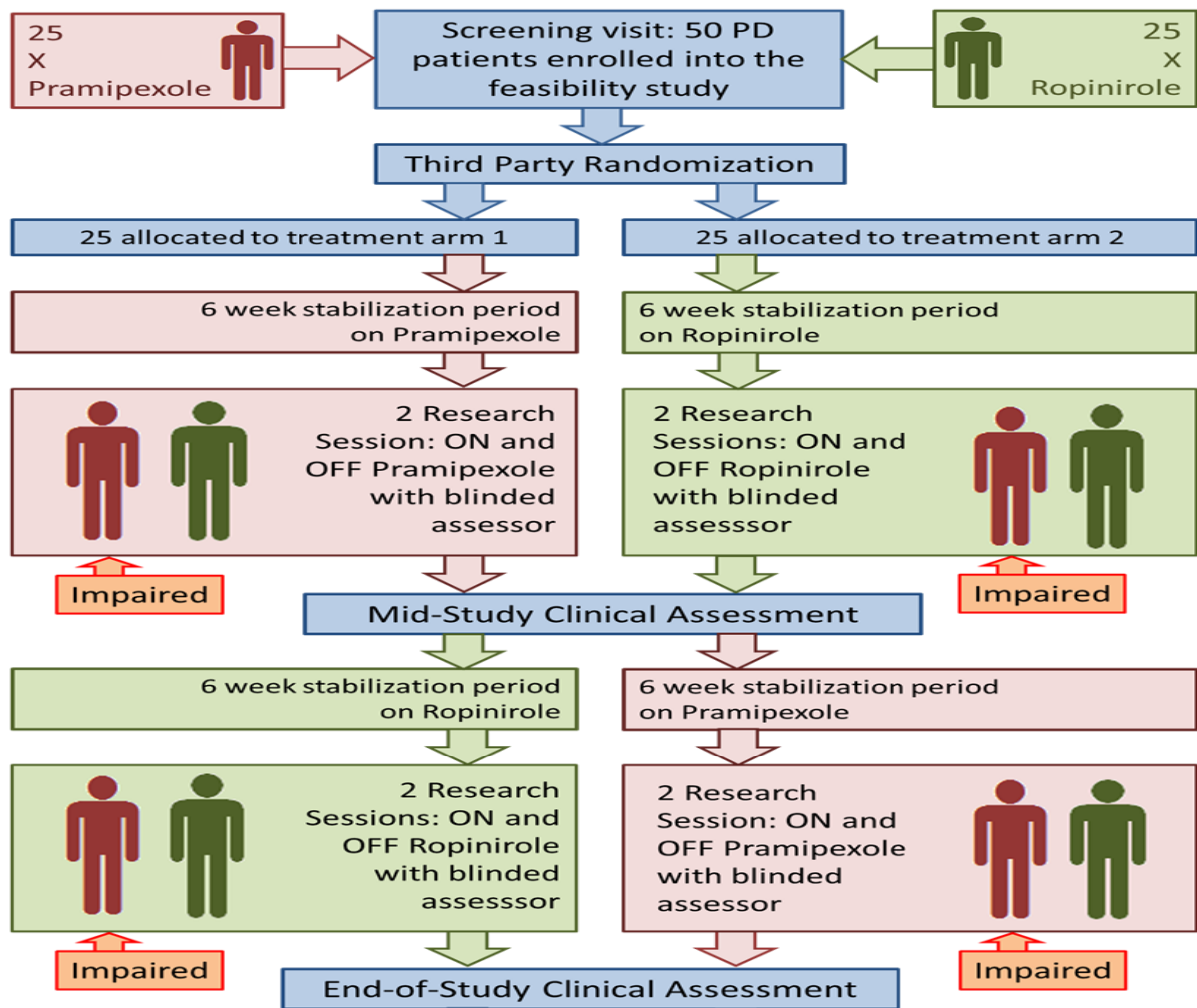


Figure 7. A schematic of which patients would be impaired if there is a phenotype effect.

The second scenario is a pure drug effect, where pramipexole induces a recollection impairment, but ropinirole does not. If this is the case, all PD patients, regardless of phenotype, will be impaired when in the ON-medication condition of the pramipexole arm, but not when in the ropinirole arm, as indicated in Figure 8.

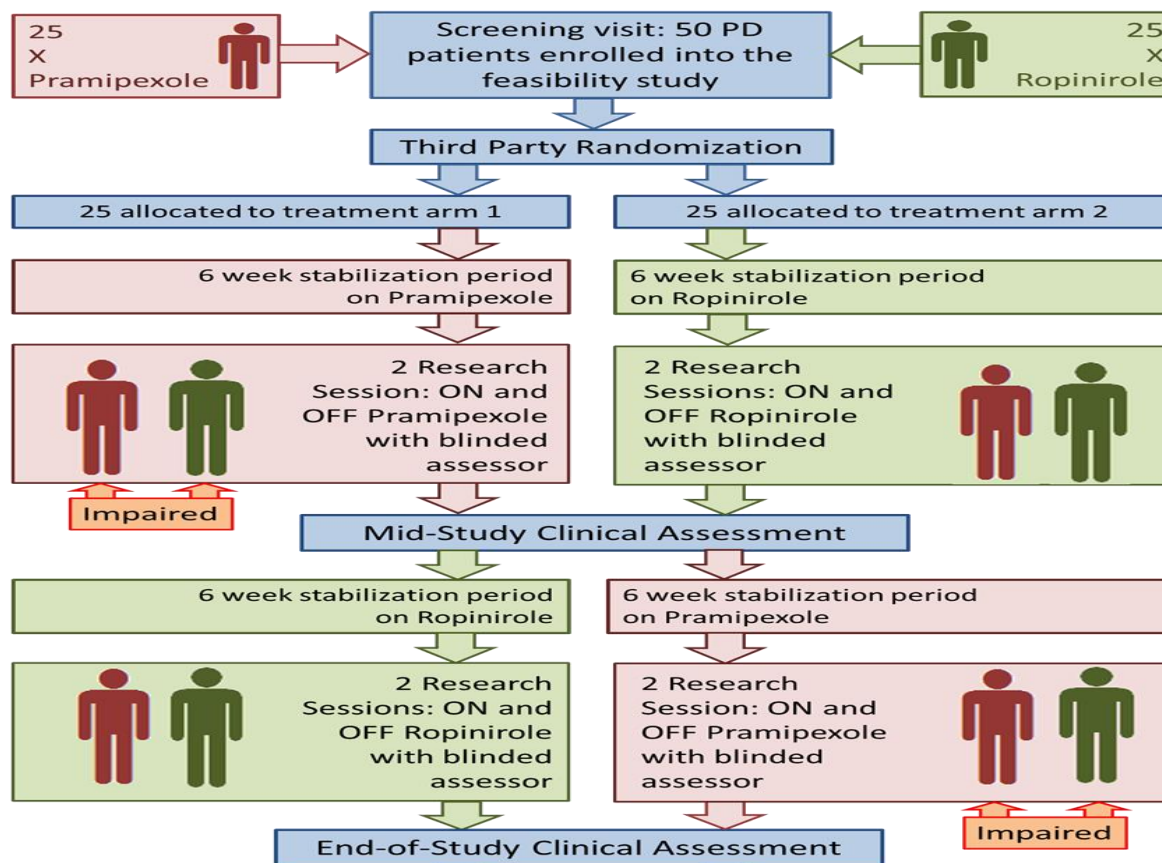


Figure 8. A schematic showing which patients would be impaired if there is a pure drug effect.

Thirdly, if scenario 3, a drug*phenotype interaction, is to be the most accurate, it would be expected that the PPX phenotype would exhibit a recollection impairment OFF-medication or when medicated with ropinirole, but this impairment is exacerbated in the ON-medication testing session in the pramipexole arm. The RPR phenotype would not show any recollection deficit, medicated with pramipexole or ropinirole as illustrated in Figure 9.

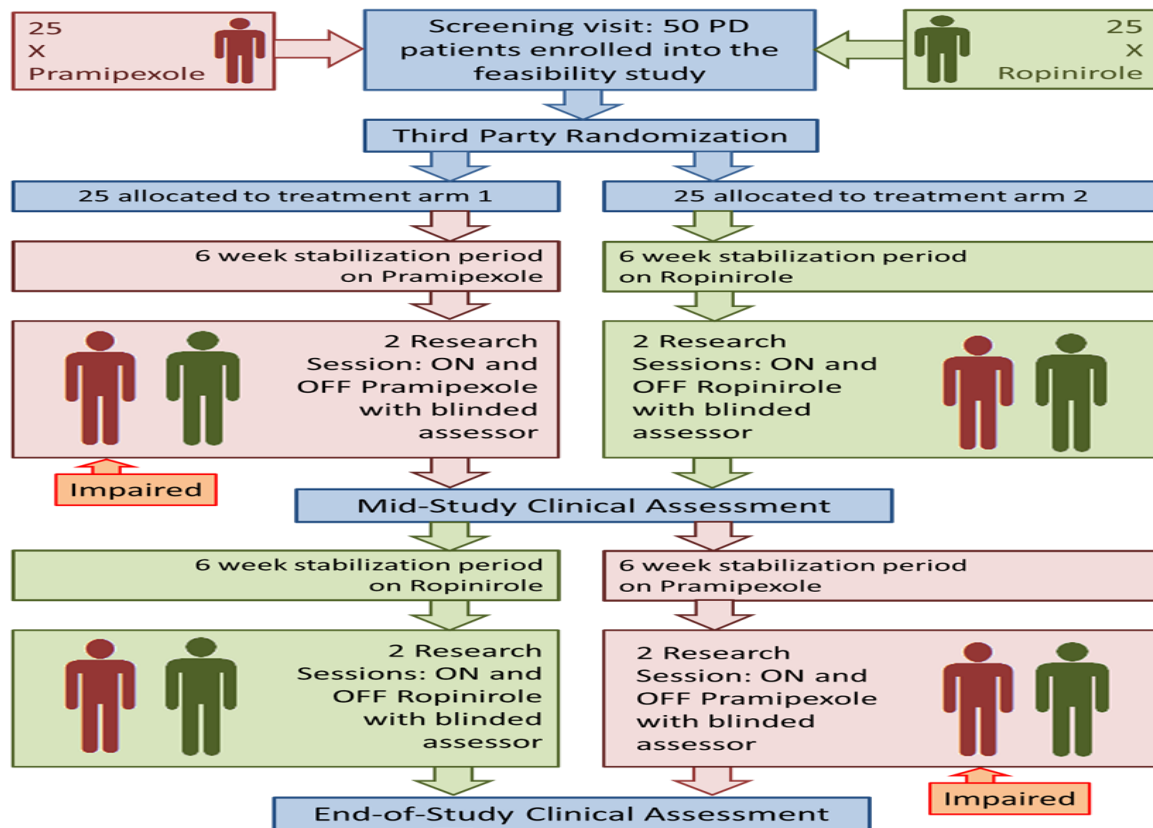


Figure 9. A schematic showing which patients would be impaired in a phenotype*drug interaction.

Another limitation of study 1 relates to the relatively small sample of PD patients included in study 1 once they are allocated to patient subgroups on the basis of their D2 dopamine agonists and the limited generalisability of the findings. Particularly in comparison to the sample sizes of the other investigations into the status of recognition memory in PD as presented in Tables 2 and 3 of this thesis. To explore whether the pattern of findings reported in study 1 are consistent in larger subgroups of PD patients, recognition memory data from study 1 will be combined with data from phase 1 of this study and reanalysed.

The study presented here is a full Clinical Trial of an Investigation Medicinal Product (CTIMP), funded by the National Institute for Health Research, Research for Patient Benefit programme (NIHR, RfPB). The trial is a single centre pilot, sponsored by the University Hospital of North Midlands and has the acronym MeMemory-PaD (**M**edication and **M**emory in **P**arkinson's **D**isease).

There is therefore a methodological focus to this chapter, which presents a pilot study, utilising a randomised controlled, crossover design to explore the contrasting effects of pramipexole and ropinirole in a single group of idiopathic PD patients. There are a number of aims of this pilot.

- i) To show how the data from this trial design be used to further explore the phenotype, drug, or phenotype*drug interaction effects which are illustrated in Figures 7, 8 and 9. To do this, the data will be presented to show how these three possibilities can be explored and p values will be provided for information.
- ii) To assess if other, more clinically accessible measures, such as immediate and delayed recall from the logical memory assessment can be used as alternative method of assessing recollective memory in clinic due to the complex and time consuming nature of obtaining recollection estimates using the remember/know procedure. To investigate the relationship between immediate and delayed recall measures with recollection, correlations will be used.
- iii) To obtain recollection estimates to inform a sample size calculation, using G*Power software, to help the design of a fully powered, definitive trial.
- iv) To combine the recognition memory data from study 1 and phase 1 of this study, to explore whether the findings reported in study 1 are found in a much larger sample of PD patients. Results were predicted to replicate those reported in study 1; familiarity would be preserved in PD and unaffected by ropinirole and pramipexole medication. Recollection was predicted to be impaired in PD compared to the HV group, ropinirole would have no effect on recollection whereas pramipexole would lead to a significant recollection impairment when compared to performance after a period of withdrawal.
- v) A further limitation of study 1 was a lack of neuropsychological assessments to measure executive functioning; therefore a fourth aims to assess the feasibility of using the neuropsychological measures included in the patient testing sessions.

- vi) To monitor recruitment to inform recruitment strategies for a fully powered, definitive trial.

4.2. Method

4.2.1. Peer review and ethics approval

The current study received independent peer review approval on the 7th of February 2011 (Appendix N). Study approval was received from the Medicines and Healthcare products Regulatory Agency (MHRA) on the 20th of November 2012 (Appendix O), and the Greater Manchester Central National Research Ethics Service (NRES) committee on the 9th of February 2013 (Appendix P).

4.2.2. Participants

4.2.2.1. Patient identification and recruitment

Parkinson's patients were identified by searching clinic notes from outpatient clinics at the Department of Neurology, University Hospital of North Midlands. Eligible patients were contacted by telephone and if in agreement, were sent an information sheet (Appendix Q). Patients opted-in to the study by returning the response form stating their interested in taking part. If an opt-in slip had not been returned by the patient after two weeks, a reminder letter was sent, however this was the last attempt by the study team to contact the patient. No return of the opt-in slip at this point was interpreted as the patient's disinterest in taking part. Recruitment information is presented in the consort diagram in Table 9.

Table 9.

Summary of PD patients identified, screened and recruited into the MeMory-PaD trial.

PD patients prescreened	220
Eligible PD patients invited to take part	81
PD patients declined to participate	31
non responders	21
Agreed to participate	28*
Screen fails	6**
Patients screened successfully	22
PD patients withdrawn	2
Discontinued due to adverse events	4
Patients completed the trial	16
 Trial recruitment rate	 29%
Trial retention rate	73%

Notes and abbreviations. * Information about one PD patient was lost by the study sponsor representative; ** 3 PD patients attended the screening who were ineligible. PD, Parkinson's disease.

4.2.2.2. Patient inclusion/exclusion criteria

In addition to the inclusion/exclusion criteria outlined in section 3.2.2.2., patients were also subject the following exclusion criteria, specific to study 2: (i) hepatic impairment (3 times upper limit of normal range); (ii) renal impairment determined by a creatinine clearance of less than 50ml/min and a glomerular filtration rate (eGFR) of less than 50 ml/minute/1.73m²; (iii) women of child bearing potential unless they are using a recognised form of contraception or are not sexually active and have no intention of becoming sexually active during the course of the trial; (iv) pre-planned or elective surgeries during the period of involvement in the trial; (v) current or planned participation in another clinical trial.

4.2.2.3. Patient participants

Sixteen patients (4 Females and 12 males; mean age = 69, SD = 8.39) with idiopathic nondementing Parkinson's Disease (UK Parkinson's Disease Society Brain Bank criteria) recruited from the Department of Neurology, University Hospital of North Midlands, completed the trial. All patients

had an existing prescription for *either* pramipexole modified release *or* ropinirole modified release and were in the mild to moderate stages of Parkinson's indicated by a mean medicated Hoehn and Yahr (1967) disease severity rating of 2.19 (SD = .51).

4.2.2.4. Healthy volunteers inclusion/exclusion criteria

HVs were assessed for eligibility on the basis of the inclusion/exclusion criteria outlined in section 3.2.2.4.

4.2.2.5. Healthy volunteer Participants

Thirteen HVs were recruited (5 Females and 8 males; mean age = 70.1, SD = 5.07). The HVs were recruited from a HV panel at the School of Psychology, Keele University. HVs were sent an invitation letter, information sheet and a response slip. Interested participants were asked to opt-in to the study by posting back the reply slip. Once this was received they were invited to take part in their first session, which took place in a private office in the School of Psychology, Keele University.

4.2.2.6. Matching patient participants and healthy volunteer groups.

Descriptive characteristic for the PD and HV groups are presented in Table 10 below.

Table 10.

Demographic and clinical characteristics of the PD patients and HVs recruited into the randomised controlled, crossover trial.

	PD phenotypes combined (n=16)		Pramipexole Phenotype (n =7)		Ropinirole Phenotype (n= 9)		Healthy Volunteers (13)	
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
	ON-Medication	OFF-Medication	ON-medication	OFF-medication	ON-medication	OFF-medication	ON/Green	OFF/Blue
Age	65.69 (8.39)	-	69 (5.89)	-	62.44 (8.88)	-	66.76 (5.88)	-
Gender	4f/12m	-	2f/5m	-	2f/7m	-	5f/8m	-
IQ	104.63 (12.10)	-	106.57 (14.14)	-	103.11 (10.89)	-	109.46 (4.39)	-
MMSE	27.50 (7.38)	-	29 (0.11)	-	29.44(0.88)	-	29.62 (0.51)	-
Hoehn and Yahr	2.16 (0.54)	2.28 (0.42)	2.29 (0.57)	2.43 (.53)	2.11 (0.49)	2.17 (0.43)	-	-
UPDRS	12.00 (4.03)	13.44 (3.93)	12.28 (4.61)	11.86 (2.54)	11.56 (4.61)	13.00 (4.12)	-	-
Epworth	8.94 (4.95)	-	8.29 (6.26)	-	9.56 (3.97)	-	2.00 (0.50)	-
Apathy	12.93 (7.60)	14.30 (9.27)	12.00(5.63)	8.67 (3.33)	13.71 (9.66)	14.75 (11.67)	8.25 (5.91)	9.75 (4.19)
l-dopa dose/day	460 (199.72)	-	300 (280.99)	-		277.78 (290.86)	-	-
Ropinirole dose/day	6.44 (2.80)	-	6.86 (1.95)	-	6.11 (3.41)	-	-	-
Pramipexole dose/day	1.70 (0.73)	-	1.80 (0.51)	-	1.63 (0.89)	-	-	-
MaoB-I dose/day	3.75 (4.10)	-	1.71 (3.68)	-	3.00(3.85)	-	-	-

Notes and abbreviations. HVs, Healthy Volunteers; LEDD , Levodopa Equivalent Daily Dose; MMSE, Mini-Mental State Examination; MaoB-I, Monoamine oxidase B Inhibitor; SD, Standard Deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

The PD patient cohort and Healthy Volunteers were matched for age ($t(27) = -.75, p = .46$), pre-morbid IQ (Weschler Test of Adult Reading [WTAR], Weschler, 2001: $t(27) = -1.73, p = .10$) and current levels of cognitive functioning (Mini-Mental Status Examination [MMSE], Folstein, Folstein & McHugh, 1975; $t(27) = .10, p = .33$).

The PD patient cohort, when medicated on each agonist were matched for motor symptom severity (Hoehn and Yahr (1967) scale [HY], $t(15) = .46, p = .65$); motor subsection of the Unified Parkinson's Disease Rating Scale [UPDRS,] Fahn & Elton, 1987: $t(15) = .70, p = .50$), daytime somnolence (Epworth Sleepiness Scale, Johns, 1991: $t(15) = -.96, p = .35$), Apathy (Starkstein's Apathy Scale, 1991; $t(15) = .27, p = .79$), low demand attention (Test of Everyday Attention: $t(15) = -2.03, p = .06$) high demand attention (Test of Everyday Attention: $t(15) = .89, p = .38$). The patient groups were also comparable on these measures after a period of withdrawal from each agonist, HY ($t(15) = .37, p = .72$), UPDRS ($t(15) = 1.31, p = .21$), Apathy ($t(15) = .86, p = .40$), low demand attention ($t(15) = -1.93, p = .07$) high demand attention ($t(15) = .30, p = .77$).

When the PD cohort were split by phenotype (PPX vs. RPR), the two patient subgroups were matched for l-dopa dose ($t(14) = -.15, p = .88$), pramipexole dose ($t(14) = -.44, p = .67$), ropinirole dose ($t(14) = -.52, p = .62$) and MaoB-I dose ($t(11) = .62, p = .55$). They were also matched for age ($t(14) = -1.90, p = .09$), IQ ($t(14) = -.55, p = .59$), MMSE ($t(14) = 1.22, p = .25$). When medicated with their own agonist the two phenotypes are match for Hoehn and Yahr disease severity stage ($t(14) = -.37, p = .72$), UPDRS ($t(14) = -.49, p = .63$), somnolence ($t(14) = .55, p = .59$) and apathy ($t(14) = .37, p = .72$). The two groups were also matched after a period of withdrawal from their medication Hoehn and Yahr ($t(14) = -1.09, p = .30$), UPDRS ($t(14) = -.49, p = .63$) and apathy ($t(14) = .12, p = .91$).

4.2.3. Design

This study was a single blind phase IV randomised controlled, crossover clinical trial and is summarised in Figure 11.

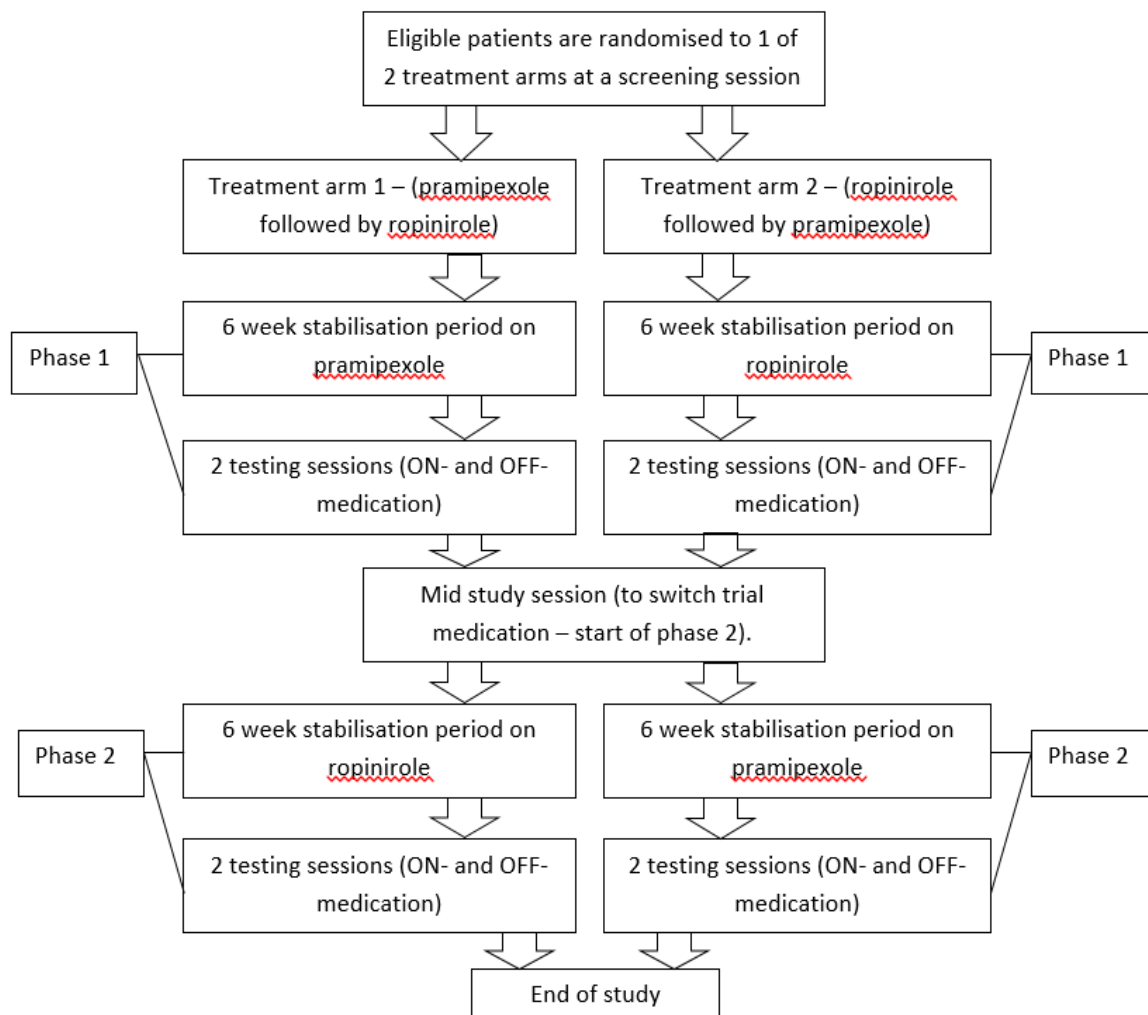


Figure 10. A flow diagram to show the randomised crossover design of study 2 and the course participants took through the trial.

PD patients were randomly allocated to 1 of 2 treatment arms, each treatment arm consists of two phases (phase 1 and phase 2). In treatment arm 1, patients were prescribed pramipexole for phase 1, tested in an ON-medication and OFF-medication condition before switching to ropinirole for phase 2 and being tested ON-medication and OFF-medication again. In treatment arm 2, patients were prescribed ropinirole for phase 1 before being switched to pramipexole for phase 2. The randomisation was conducted by a third party programme at a ratio of 1:1 - unaffected by the agonist patients were taking before they entered the trial (e.g., a patient taking ropinirole before entering the trial had a 50% chance of being allocated to treatment arm 1 and needing to switch to pramipexole for phase 1 before switching back to ropinirole for phase 2, and a 50% chance of being

allocated to treatment arm 2 and not needing to switch to pramipexole until after phase 1 had been completed). The order of the ON-medication and OFF-medication testing sessions were counterbalanced across participants and treatment arms. The researcher was blinded to the treatment arm of each patient, but not to whether they were being tested ON- or OFF-medication.

HVs were also tested in 2 separate research sessions labelled “green” and “blue” to signify the absence of the ON-/OFF-medication manipulation. The “green” session was yoked to the patient’s ON-medication session and the “blue” session to the “OFF-Medication” session.

4.2.3.1. Dosage equivalents for switching trial medication

Dosage guidelines (Lyons and Pahwa, 2009) suggest that the most clinically efficient conversion rate when switching between pramipexole extended release and ropinirole modified release is 4mg of ropinirole to 1mg of pramipexole (base). Dosage conversion rates and the nearest available pramipexole dosage are presented in Table 11 (ropinirole is available in 2mg, 4mg and 6mg sized dosages). These conversion equivalents were adhered to as closely as possible throughout the trial unless a patient experienced dose dependent side-effects in which case the dose was reduced by the smallest increments possible.

Table 11.

Dosage conversion for switching between ropinirole and pramipexole.

Medication	Converted Dosage (Mgs)					
Ropinirole	2	4	6	8	10	12
Pramipexole	0.5	1	1.5	2	2.5	3
Available Pramipexole dose tablets	0.52	1.05	1.57 (0.52+1.05)	2.1	2.62 (0.52+2.1)	3.1

Notes and abbreviations. Mgs, milligrams per day.

4.2.3.2. Medication withdrawal

To examine medication effects, patients were tested ON- and OFF-medication in both phases of each treatment arm. For the OFF-medication testing sessions, patients were tested after a period of withdrawal to reflect 4 half-lives of each agonist, resulting 93.75% elimination of each agonist. The half-life of ropinirole modified release is 8 hours requiring a withdrawal period of 32 hours before the OFF-medication testing session, whereas the half-life for pramipexole extended release is 12 hours resulting in a withdrawal period of 48 hours prior to OFF-medication testing. Adjuvant therapies of l-dopa preparations and monoamine oxidase-B inhibitors have a half-life of 3 hours therefore the last dosages of these were taken 12 hours prior OFF-medication testing sessions. Instructions were given to patients, about how to switch, on a study card (Appendix R).

4.2.4. Stimuli

4.2.4.1. Mini Mental Status Examination

See section 3.3.4.1.

4.2.4.2. Unified Parkinson's Disease Rating Scale – Motor subsection

See section 3.3.4.3

4.2.4.3. Epworth Sleepiness Scale

See section 3.3.4.4.

4.2.4.4. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS, Appendix S) (Zigmond & Snaith, 1983) is a fourteen item, self-report scale, 7 items relate to anxiety and 7 to depression. Each item (e.g., 'I still enjoy the things I used to enjoy') is scored on a 4 point scale ranging from 0 (e.g., 'Not at all') to 3 (e.g., 'Definitely as much'). The HADS was included in study 2 over other measure of depression and

anxiety as it avoids relying on features of depression and anxiety that are also somatic features of other illnesses, such as fatigue, insomnia and hypersomnia (Zigmond & Snaith, 1983).

4.2.4.5. Recognition memory test

Four versions of a two stage “yes/no” recognition memory test were produced (“RM-Test1”, “RM-Test2”, “RM-Test3” and “RM-Test4”) from a pool of 400 nouns and divided into 8 lists of 50 words matched for imageability (list-1, mean 5.08, SD 1.37; list-2, mean 25.07, SD 1.48; list-3, mean 5.10, SD 1.26; list-4, mean 5.08, SD 1.4; list-5, 5.03, SD 1.25; list-6, mean 5.06, SD 1.25; list-7, mean 5.13, SD 1.18; list-8, mean 4.91, SD 1.33), concreteness (list-1, mean 5.4, SD 1.47; list-2, mean 5.39, SD 1.45; list-3, 5.38, SD 1.46; list-4, mean 5.40, SD 1.47; list-5, mean 5.4, SD 1.17; list-6, mean 5.23, SD 1.29; list-7, mean 5.34, SD 1.23; list-8, mean 5.27, SD 1.28) and frequency (list-1, mean 62.06, SD 69.09; list-2, mean 62.76, SD 69.48; list-3, mean 61.9, SD 69.77; list-4 mean 64.4, SD 69.45; list-5, mean 63.44, SD 71.3; list-6, mean 61.2, SD 73.39; list-7 mean 61.14, SD 97.15; list-8, mean 62.37, SD 83.67, Toronto noun pool; Franklin, Hoffman & Rubin, 1982). The 8 lists were then randomly assigned as either target or distractor items of each of the four tests. The order of RM-Test1, RM-Test2, RM-Test3 and RM-Test4 were counterbalanced across treatment arms and ON-medication/green and OFF-medication/blue conditions (see Appendix K, for the words that complied the 8 lists and an illustration of the comparability of RM-Test1, RM-Test2, RM-Test3 and RM-Test4).

4.2.4.6. Hayling sentence completion task

The Hayling sentence completion task (Appendix T) (Burgess & Shallice, 1997) is comprised of two separate sections; initiation and suppression. In the initiation section, participants are read 15 independent sentences, each with the last word missing (e.g., ‘he posted a letter without a ...’). The participant is instructed to suggest a word which appropriately completes the sentence (e.g., ‘stamp’) as quickly as they can. The time it takes the participant to suggest each word is recorded as a simple measure of response initiation speed. In the suppression section, instead of suggesting an appropriate word to complete the sentence participants must suggest a word which is completely

unconnected to the sentence (e.g., 'the captain wanted to stay with the sinking ... curtain'). This task requires the suppression of a habitual response (e.g., ship) followed by the generation of an atypical one. Suggestions are given one of three ratings by the experimenter, either correct (if the suggested word is completely unconnected to the sentence), category A error (if the suggested word appropriately completes sentences) or a category B error (if the suggested word is partially connected to the sentence). This section of the task provides a measure of response suppression, as a result of the time it takes for the participant to generate the word and an error score based on the number of category A and category B errors. The Hayling sentence completion task was included in study 2 as a measure of prefrontal dependent cognitive control and executive function.

4.2.4.7. Test of Everyday Attention

Two subsets of the Tests of Everyday Attention (TEA, Appendix U) (Robertson, Ward, Ridgeway & Nimmo-Smith, 1994) were administered; Elevator Counting and Elevator Counting with Distraction, both of which are played on an audio CD. In the Elevator Counting task participants are instructed to imagine they are in a ground floor elevator but the visual floor indicator is broken. As the elevator passes each floor a tone sounds and participants are instructed to count the tones until asked 'how many?' as if to describe what floor the elevator would now be at. The tones sound at an irregular tempo. Two practice items are completed prior to the main task so that participants are familiarized with the tones.

The Elevator Counting with Distraction Task participants are instructed to count the tones as they had done in the previous task, but to also ignore a distractor tone of a higher frequency. Two practice items are completed to demonstrate the difference between the two tones. These subsets of the TEA are included as a measure of participant's attentional resources and cognitive control.

4.2.4.8. Apathy Scale

The Apathy scale (Appendix V) (Starkstein, Mayberg, Preziosi, Andrezejewski, Leiguarda, & Robinson, 1992) is a self-report questionnaire consisting of 14 items, which are formulated as questions (e.g., 'Are you interested in new things?') and are read by the experimenter. The participants chooses 1 of four responses ranging from "not at all" to "a lot". For Questions 1 to 8, the "not at all" answer corresponds to high levels of apathy, whilst for questions 9 to 14 "not at all" corresponds to low levels.

4.2.4.9. Logical Memory Test

See section 3.3.4.10.

4.2.4.10. Wechsler Test of Adult Reading

See section 3.3.4.5.

4.2.4.11. Working Memory

See section 3.3.4.9.

4.2.5. Apparatus

A Dell laptop with a 15" screen was used to present the recognition memory task and to play the audio CD for the TEA (Robertson et al., 1994). A stop watch used to time participant response for the Hayling sentence completion task (Burgess and Shallice, 1997).

4.2.6. Procedure

4.2.6.1. Trial procedure

Eligible patients who had opted in to the study attended a screening at the Guy Hilton Research Centre, University Hospital of North Midlands (UHNM), with a consultant neurologist (SJE) and a neurology research nurse. Informed consent (Appendix W) was received from all patients

during the screening session before any study procedures commenced. The MMSE and a functional assessment of mental capacity were completed (SJE) and vital signs (blood pressure, pulse, respiration rate, temperature and weight) were recorded. Blood tests were taken to assess renal and hepatic function if no data existed in the patient's medical records from within the last 3 months. The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) and the Modified Hoehn and Yahr (1967) severity scale were completed. Once a patient had been enrolled into the study they were randomised to a treatment arm (as described in section 4.2.4.) and given an 8 week prescription of their trial medication (generic form) from the pharmacy, UHNM. Patients were also given a study card (Appendix R) which contained instructions about how to withdraw from their medication appropriately for the OFF-medication session. All patients had a 6 week stabilisation period on the trial medication before the phase 1 ON-medication and OFF-medication testing sessions.

Once both phase 1 testing sessions had been completed patients had a mid-study visit at the Guy Hilton Research Centre, UHNS, with a consultant neurologist (SJE) and a neurology research nurse. At the mid study visit, vital signs were recorded. The Mini-Mental Status Examination (Folstein et al, 1975) was also re-administered – to ensure patients still conformed to the inclusion/exclusion criteria. A Hoehn and Yahr (1967) and UPDRS (Fahn and Elton, 1987) motor exam was also completed. Patients switched trial medication (ropinirole to pramipexole, *or* pramipexole to ropinirole depending on the treatment arm), given an 8 week prescription of their phase 2 trial medication from the pharmacy, UHNS and a second study card documenting the instructions of how to appropriately withdraw their medication for the phase 2 OFF-medication testing session.

Patients were then given another 6 week stabilisation period on their phase 2 trial medications before engaging in the ON- and OFF-medication testing sessions. Once these were completed patients had an end of study at the Guy Hilton Research Centre, UHNS, with a consultant neurologist (SJE) and neurology research nurse. Vital signs were recorded, and the Hoehn and Yahr

(1967) and the UPDRS (Fahn & Elton, 1987) assessments were completed. During this end of study visit, data from both trial medications and the patient's subjective experience of each drug were used to discuss which offered the best clinical management and which was best tolerated in terms of side-effects. This offered patients the opportunity to revert back to the dopamine agonist they were taking as they entered the study or, to change to the alternative.

4.2.6.2. Testing session procedure

Patient-Participants took part in 4 separate research sessions, phase 1 ON-medication and OFF-medication and phase 2 ON-medication and OFF-medication. Each testing session started at 9:00am, to avoid time of day effects and took place in the patient's home for convenience – especially during the OFF-medication sessions. Every session began with an overview of what would be done in that session and participants were reminded they could take breaks when necessary. Participants were sat at a table in front of a laptop screen. Operation of the laptop was carried out by the experimenter due to the motor symptoms of the patient group. All sessions contained a recognition memory test, the TEA (Robertson et al, 2004), The Logical Memory Test (Wechsler, 1997), Apathy Scale (Sharkstein et al, 1992) Working Memory task (Wechsler, 1997), the Hayling Sentence Completion task (Burgess and Shallice, 1997), a physical exam for the Hoehn and Yahr (1967) and UPDRS (Fahn & Elton, 1987) disease severity measures. The ESS (Johns, 1991) was only completed in the ON-Medication session, and the WTAR (Wechsler, 2001) was administered in the first (phase 1) ON-Medication only.

4.2.6.3. Two stage yes/no recognition memory test

See section 3.3.6.2.

4.3. Results

The results from this study are divided into sections to show how the data can be analysed to explore the three possible scenarios discussed in section 4.1.

In section 4.3.1., to explore for a phenotype effect, the PD cohort is divided into two groups based on their phenotype (RPR or PPX) and analysed ON- and OFF- the medication that they were taking prior to entering the trial. Data is then compared to the HVs.

In section 4.3.2., to explore for a drug effect performances ON- and OFF- ropinirole and pramipexole are compared with the PD cohort grouped into a single cohort using a within groups analysis, and compared to HVs.

To explore for a phenotype*drug interaction, in section 4.3.3., the PD cohort are divided into two subgroups based on the PPX or RPR phenotype and their respective performances ON- and OFF- on pramipexole and ropinirole are compared. The two PD phenotypes are then compared to the HVs.

In section 4.3.5. data from study 1 and phase 1 of study 2 are combined to explore the impact of ropinirole and pramipexole on recognition memory, familiarity and recollection with a greater statistical power.

Homogeneity of variance within each condition was confirmed by a series of Levene's tests for each outcome measure (RM, familiarity and recollection), in each of the four medication conditions (ON- and OFF-medication in the ropinirole arm and ON- and OFF-medication in the pramipexole arm). RM in the ropinirole arm, ON-medication ($F = 3.58, p = .07$), OFF-medication ($F = 2.32, p = .14$) and in the pramipexole arm, ON-medication ($F = 1.03, p = .32$) and OFF-medication ($F = 1.53, p = .22$). Familiarity in the ropinirole arm, ON-medication ($F = .58, p = .45$), OFF-medication ($F = .54, p = .47$) and in the pramipexole arm, ON-medication ($F = .30, p = .59$) and OFF-medication ($F = .22, p = .65$). Recollection in the ropinirole arm, ON-medication ($F = .87, p = .36$), OFF-medication ($F =$

.19, $p = .67$) and the pramipexole arm, ON-medication ($F = .20$, $p = .66$) and OFF-medication ($F = 1.01$, $p = .32$).

The normality of the distribution of the RM, familiarity and recollection estimates from all conditions was confirmed with a series of Shapiro-Wilk tests; The RM data was normally distributed in participants when medicated with ropinirole, ON-medication ($p = .13$), OFF-medication ($p = .27$) and when medicated with pramipexole, ON-medication ($p = .14$) and OFF-medication ($p = .14$). The familiarity data was also normally distributed in the participants when in the ropinirole arm, ON-medication ($p = .24$), OFF-medication ($p = .53$) and in the pramipexole arm, ON-medication ($p = .37$), OFF-medication ($p = .59$). The recollection data was also normally distributed in the ropinirole arm, ON-medication ($p = .31$), OFF-medication ($p = .31$) and in the pramipexole arm, ON-medication ($p = .35$) and OFF-medication ($p = .04$). As the subgroups are relatively modest in sample size the data was also manually checked for outliers using Q-Q and box plots, no data was omitted. As a result of the robust statistical evidence of the normality of the data distribution and homogeneity of variance, parametric testing was conducted even though the total $N = 16$ for within-groups analysis was close to the required threshold of 15, as recommended by Kitchen (2009).

4.3.1. Scenario 1 – a phenotype effect

The raw hit and false alarm means and standard deviations for RM, *know* and *remember* responses from the PD group (all PD patients, on their usual dopamine agonist), and the HVs, are presented by ON- and OFF-Medication conditions in Table 12. Estimates of RM (d'), familiarity (d') and recollection (pr) are presented in Figure 11.

Table 12.

Means and standard deviations for raw hits and false alarms for recognition memory, know and remember for PD patients compared to Healthy Volunteers from the ON-medication/green and OFF-medication conditions.

	PD Patients (n = 16)		Healthy Volunteers (n = 13)	
	Means (SD)		Means (SD)	
	ON-medication	OFF-medication	ON/Green	OFF/BLUE
Recognition memory				
Hits	32.69 (7.60)	32.07 (8.32)	37.38 (6.49)	36.62 (6.95)
False Alarms	5.25 (4.09)	5.19 (4.48)	3.85 (2.88)	4.92 (3.86)
<i>d'</i>	1.95 (.55)	1.87 (.54)	2.15 (.58)	1.99 (.53)
Know				
Hits	13.00 (6.09)	10.94 (6.67)	9.61 (4.13)	8.15 (3.11)
False Alarms	3.38 (2.85)	2.44 (2.16)	2.62 (2.32)	2.23 (1.69)
<i>d'</i>	1.45 (.52)	1.41 (.58)	1.53 (.63)	1.47 (.63)
Remember				
Hits	19.69 (7.13)	21.13 (7.96)	27.00 (6.76)	28.62 (6.55)
False Alarms	1.88 (2.06)	2.75 (2.67)	1.08 (1.04)	2.69 (3.66)
<i>Pr</i>	.43 (.16)	.44 (.17)	.52 (.14)	.54 (.14)

Notes and abbreviations. PD = Parkinson's Disease; SD = Standard Deviation *d'*, signal detection measure of discrimination accuracy; *pr*, threshold measure.

The RM (*d'*), familiarity (*d'*) and recollection (*pr*) were analysed separately using a series of 2 X 2 Mixed ANOVAs, with a between factor of Group (PD group vs. HVs) and a within-subjects factor of Medicated State (ON-medication vs. OFF-medication). Significant main effects were further explored with pairwise comparisons, with a Bonferroni correction to control for type I error. Analysis of RM (*d'*) revealed no significant effect of Group ($F(1, 27) = 2.80, p = .11$), Medicated State ($F(1, 27) = .89, p = .35$), or the Group*Medicated State interaction ($F(1,27) = .47, p = .50$).

Further 2 X 2 ANOVAs of familiarity (*d'*) data revealed no significant effect of Group ($F(1,27) = .44, p = .52$), Medicated State ($F(1,27) = .10, p = .76$) or the Group*Medicated State interaction ($F(1,27) = .07, p = .79$).

Analysis of estimates of recollection (*pr*) revealed a significant main effect of Group ($F(1,27) = 13.05, p < .001$). Pairwise comparisons with a Bonferroni correction revealed that a significant

recollection impairment in the PD group was present in both the ON-Medication ($p = .003$) and OFF-Medication ($p = .002$) conditions. No significant effect of Medicated State ($F(1,27) = .87, p = .36$) was found and the Group*Medicated State interaction was also not significant ($F(1,27) = .13, p = .72$).

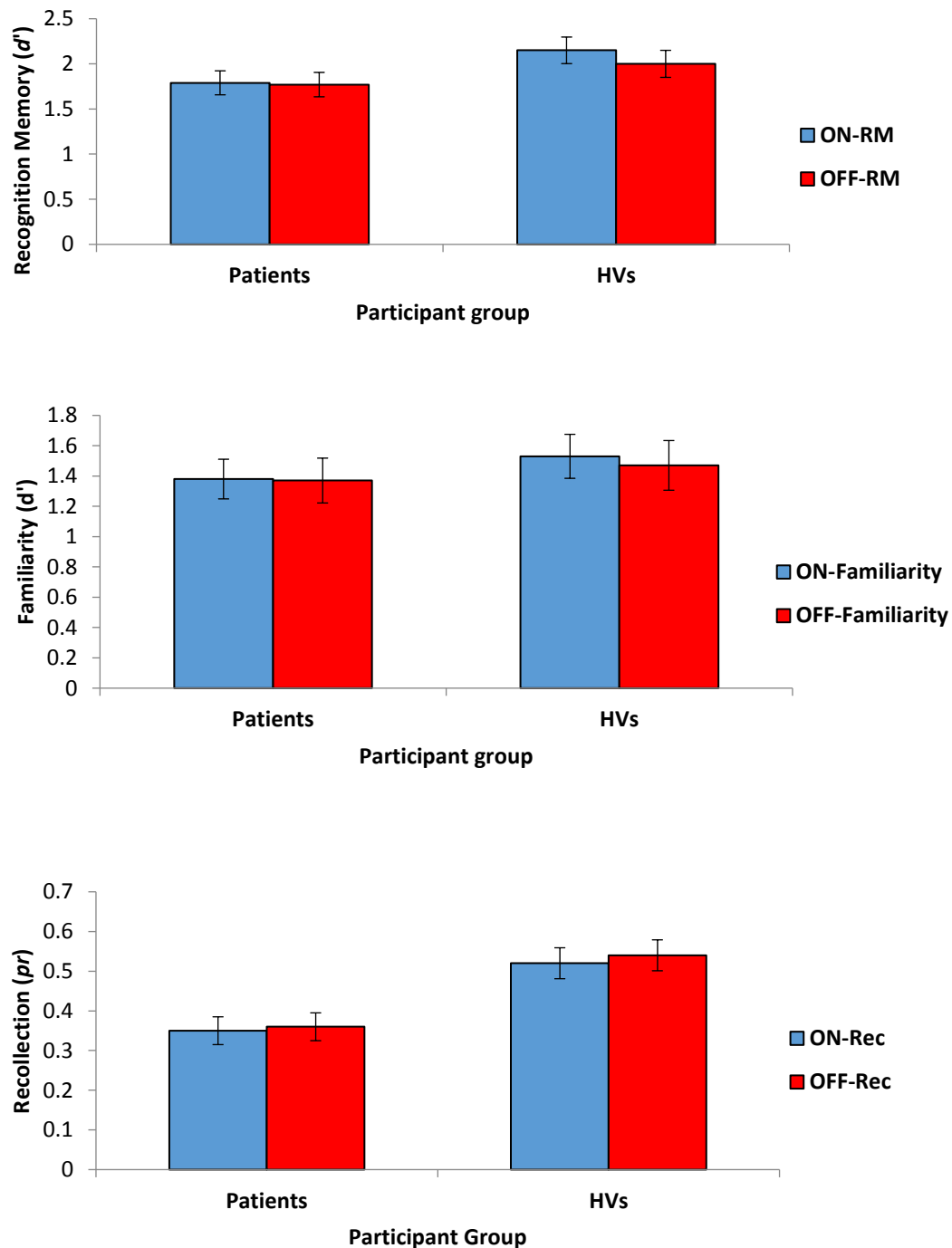


Figure 11. Estimates of recognition memory (top), familiarity (middle) and recollection (bottom) for both ON-medication/Green and OFF-medication/Blue conditions by participant group. *Notes and abbreviations.* Error bars represent the standard error of the mean. HVs, Healthy volunteers; ON, medicated; OFF, unmedicated; RM, recognition memory; Rec, Recollection.

This initial set of analysis shows that when the PD patients in a whole cohort, and tested ON and OFF the medication that they take as part of their usual regimen, overall recognition memory and familiarity are comparable to the HV performance both ON- and OFF-medication. However,

recollection was significantly impaired when both ON- and OFF-medication. Recognition memory, familiarity and recollection performance were all unaffected by medication. This series of findings are consistent with the findings of study 1 (see chapter 3). To explore this further, like in study 1 the PD cohort was then divided into two subgroups based on original PD medication prior to entering the trial (PPX and RPR), the results are presented in the section below.

The raw hit and false alarm means and standard deviations for RM, *know* and *remember* responses from the PD subgroups (PD group divided by phenotype PPX and RPR) from the ON-medication and OFF-medication conditions are presented in Table 13. Estimates of RM (d'), familiarity (d') and recollection (pr) are presented in Figure 12. The data were analysed separately using a series of 3 X 2 Mixed ANOVAs, with a between factor of Group (RPR vs. PPX vs. HVs) and a within-subjects factor of Medicated State (ON-Medication vs. OFF-Medication). Significant main effects were further explored using pairwise comparisons, with a Bonferroni correction to control for type I error.

Table 13.

Means and standard deviations for raw hits and false alarms for recognition memory, know and remember by group and condition.

	PD Patient Group (n = 16)				Healthy Volunteers (n = 13)	
	Pramipexole (n = 7)		Ropinirole (n = 9)			
	Mean (SD)		Mean (SD)		Mean (SD)	
	ON-medication	OFF-medication	ON-medication	OFF-medication	ON/Green	OFF/BLUE
<i>Recognition memory</i>						
Hits	31.00 (7.19)	31.71 (9.03)	34.00 (8.08)	32.33 (8.28)	37.38 (6.49)	36.62 (6.95)
False Alarms	5.71 (3.59)	7.57 (7.96)	4.89 (4.62)	3.33 (3.20)	3.85 (2.88)	4.92 (3.86)
<i>d'</i>	1.69 (.40)	1.65 (.54)	1.94 (.55)	2.00 (.60)	2.15 (.58)	1.99 (.53)
<i>Know</i>						
Hits	13.43 (8.18)	9.14 (5.87)	12.67 (4.39)	12.33 (7.25)	9.61 (4.13)	8.15 (3.11)
False Alarms	4.29 (3.40)	3.43 (2.07)	2.67 (2.29)	1.67 (2.00)	2.62 (2.32)	2.23 (1.69)
<i>d'</i>	1.24 (.44)	1.28 (.72)	1.54 (.41)	1.64 (.57)	1.53 (.63)	1.47 (.63)
<i>Remember</i>						
Hits	17.57 (6.45)	2.98 (7.89)	21.33 (7.57)	20.00 (8.29)	27.00 (6.76)	28.62 (6.55)
False Alarms	1.43 (1.27)	4.14 (3.18)	2.22 (2.54)	1.67 (1.66)	1.08 (1.04)	2.69 (3.66)
<i>pr</i>	.33 (.14)	.37 (.14)	.38 (.15)	.36 (.15)	.52 (.14)	.54 (.14)

Notes and abbreviations. PD, Parkinson's Disease; SD, Standard Deviation; *d'*, signal detection measure of discrimination accuracy; *pr*, threshold measure.

For the RM (d') data, the first 3 X 2 ANOVA, revealed a significant effect of Group ($F(2, 26) = 3.44, p = .04$). Pairwise comparison revealed that RM was significantly impaired in the PPX subgroup in the ON-Medication condition compared to HVs ($p = .03$) but not the RPR subgroup ($p = .22$) and that no significant difference between the RPR subgroup and the HVs emerged ($p = .36$). In the OFF-Medication condition, RM in the PPX subgroup was significantly impaired compared to the HVs ($p = .04$), and approached significance compared to the RPR subgroup ($p = .05$). The RPR and HVs did not significantly differ ($p = .98$). No significant main effect of Medicated State ($F(1,26) = .59, p = .45$) or Group*Medicated State interaction ($F(2,26) = .50, p = .62$) were found.

For familiarity (d') data there were no significant effects of Group ($F(2,26) = 2.44, p = .11$) or Medicated State ($F(1,26) = .10, p = .76$). Similarly no significant Group*Medicated State interaction ($F(2,26) = .39, p = .68$) was found.

Analysis of recollection estimates (pr) revealed a significant main effect of Group ($F(2,26) = 6.44, p = .005$). Further exploration of this effect, using pairwise comparisons, showed that in the ON-medication condition, recollection in the RPR subgroup and the PPX subgroup were both significantly impaired compared to controls ($p = .03$ and $p = .005$, respectively). No significant differences emerged between the RPR and PPX subgroups ON-medication ($p = .40$) or OFF-medication ($p = .99$), however, OFF-medication, both RPR and PPX subgroups are significantly impaired compared to the HVs ($p = .007$ and $p = .01$, respectively). There was no significant main effect of Medicated State ($F(1,27) = .85, p = .37$) and no significant Group*Medicated State interaction ($F(2,26) = .73, p = .49$) was found.

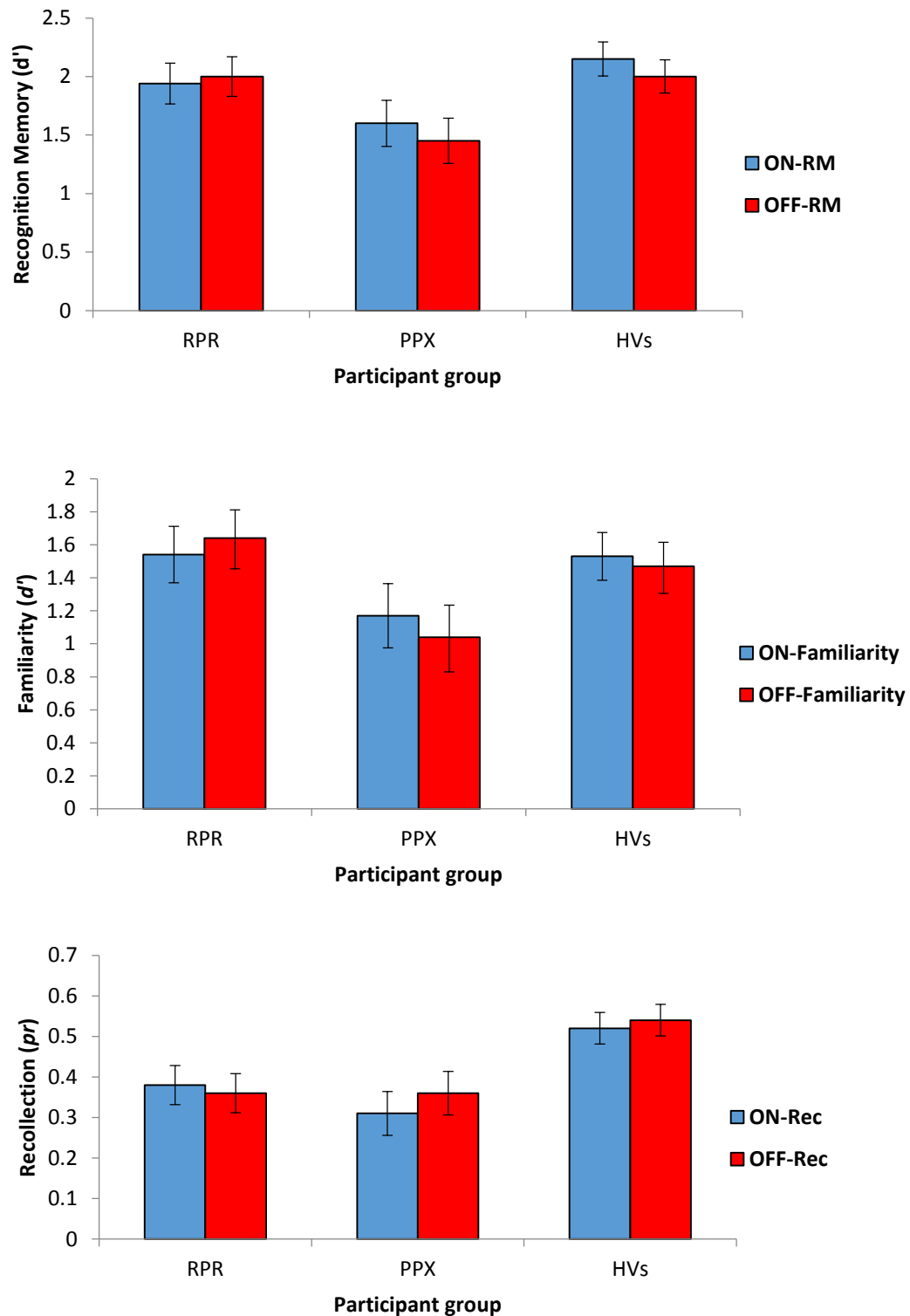


Figure 12. Estimates of recognition memory (top), familiarity (middle) and recollection (bottom) for both ON-medication/Green and OFF-medication/Blue conditions by participant group. *Note and abbreviations.* Error bars represent the standard error of the mean. HVs, Healthy volunteers; ON, medicated; OFF, unmedicated; RM, recognition memory; Rec, Recollection; RPR, Ropinirole; PPX, Pramipexole.

In summary, familiarity was comparable to the HVs both ON and OFF medication, and was unaffected by ropinirole or pramipexole. Recollection was significantly poorer in both the PPX and RPR phenotypes compared to the HVs, in both the medicated and unmedicated conditions, not difference between the two PD subgroups emerged. No significant differences were found between the ON and OFF-medication conditions in the PPX and RPR phenotypes, although there was a trend for recollection to decline when in the ON-medication condition, consistent with study 1.

The results presented so far have focused on analyses of patient data ON and OFF their typical daily dopamine agonist. The following section presents the results from the whole PD cohort tested on dopamine agonists, ropinirole *and* pramipexole, to fully explore the effects of each drug in the same PD patients.

4.3.2. Scenario 2 - a drug effect

The raw hit and false alarm means and standard deviations for RM, *know* and *remember* responses from the PD subgroups (PD group split by their pre-trial agonist, RPR and PPX) from the ON-medication and OFF-medication conditions are presented in Table 13. Estimates of RM (d'), familiarity (d'), recollection (pr) and delayed recall are presented in Figure 14. To compare the effect of ropinirole and pramipexole in the whole PD cohort, RM (d'), familiarity (d') and recollection (pr) estimates were analysed separately using a series of 2 X 2 ANOVAs with two within groups factors Drug (ropinirole vs. pramipexole) and Medicated State (ON-medication vs. OFF-medication). Following these analyses, independent *t*-tests were used to compare the RM estimates of the PD group with HVs, across Drug and Medicated State conditions.

Table 14.

Means and standard deviations for raw hits and false alarms for recognition memory, know and remember by group and condition

	PD Patient Group (n = 16)				Healthy Volunteers (n = 13)	
	Pramipexole		Ropinirole			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	ON-medication	OFF-medication	ON-medication	OFF-medication	ON/Green	OFF/BLUE
<i>Recognition memory</i>						
Hits	34.00 (7.93)	32.44 (8.97)	31.44 (9.38)	29.81 (8.85)	37.38 (6.49)	36.62 (6.95)
False Alarms	5.56 (4.27)	5.00 (3.95)	2.25 (4.49)	3.63 (2.90)	3.85 (2.88)	4.92 (3.86)
<i>d'</i>	1.80 (.54)	1.86 (.59)	1.65 (.64)	1.77 (.59)	2.15 (.58)	1.99 (.53)
<i>Know</i>						
Hits	14.69 (8.57)	10.88 (5.54)	12.56 (5.67)	11.12 (6.75)	9.61 (4.13)	8.15 (3.11)
False Alarms	4.25 (3.92)	2.87 (2.39)	3.12 (2.42)	1.81 (2.07)	2.62 (2.32)	2.23 (1.69)
<i>d'</i>	1.40 (.54)	1.44 (.67)	1.26 (.51)	1.44 (.54)	1.53 (.63)	1.47 (.63)
<i>Remember</i>						
Hits	19.31 (7.92)	21.56 (7.86)	18.88 (7.94)	18.69 (8.01)	27.00 (6.76)	28.62 (6.55)
False Alarms	1.31 (.95)	2.13 (2.31)	2.12 (2.60)	1.81 (1.51)	1.08 (1.04)	2.69 (3.66)
<i>pr</i>	.36 (.15)	.39 (.15)	.32 (.17)	.33 (.15)	.52 (.14)	.54 (.14)

Notes and abbreviations. PD, Parkinson's Disease; SD, Standard Deviation; *d'*, signal detection measure of discrimination accuracy; *pr*, threshold measure.

To compare the effect of ropinirole and pramipexole in the whole PD cohort, RM (d'), familiarity (d') and recollection (pr) estimates were analysed separately using a series of 2 X 2 ANOVAs with two within groups factors, Drug (ropinirole vs. pramipexole) and Medicated State (ON-Medication vs. OFF-Medication). Following these analyses, independent t -tests were used to compare the RM estimates of the PD group with HVs, across Drug and Medicated State Conditions.

Analysis of RM (d') data revealed no significant main effect of Drug ($F(1,15)$, = .45, p = .51), Medicated State ($F(1,15)$, = .70, p = .42) and the interaction of Drug*Medicated State ($F(1,15)$, = .18, p = .68). When medicated with ropinirole, RM estimates in the PD group were significantly lower than the HVs in the ON-medication condition ($t(27)$, = -2.18, p = .04), but not in the OFF-medication condition ($t(27)$, = -1.08, p = .29). When medicated with pramipexole, the PD group's RM performance was poorer than that of the HVs in the ON-medication condition, but only approached significance ($t(27)$, = -1.91, p = .07) and was comparable when OFF-medication ($t(27)$, = -1.03, p = .31).

Analysis of Familiarity (d') estimates revealed no significant main effects of Drug ($F(1,15)$, = .01, p = .93, or Medicated State ($F(1,15)$, = .75, p = .40) and the interaction of Drug*Medicated State was also not significant ($F(1,15)$, = 1.79, p = .20). Familiarity estimates of the PD group were comparable to the HVs across all testing conditions; when medicated with ropinirole, ON-medication ($t(27)$, = -1.28, p = .21), OFF-medication ($t(27)$, = -.16, p = .88), and when medicated with pramipexole, ON-medication ($t(27)$, = -.73, p = .47) and OFF-medication ($t(27)$, = -.60, p = .55).

For Recollection (pr) estimates, analysis revealed no significant main effect of Drug ($F(1,15)$, = 2.84, p = .11), or Medicated State ($F(1,15)$, = 1.51, p = .24) and the interaction of Drug*Medicated State was also not significant ($F(1,15)$, = .30, p = .60). There was a significant Recollection deficit in the PD group compared to HVs; when medicated with ropinirole, ON-medication ($t(27)$, = -3.40, p = .002), OFF-medication ($t(27)$, = -3.91, p < .001) and when medicated with pramipexole ON-medication ($t(27)$, = -2.30, p = .007) and OFF-medication ($t(27)$, = -2.81, p = .009).

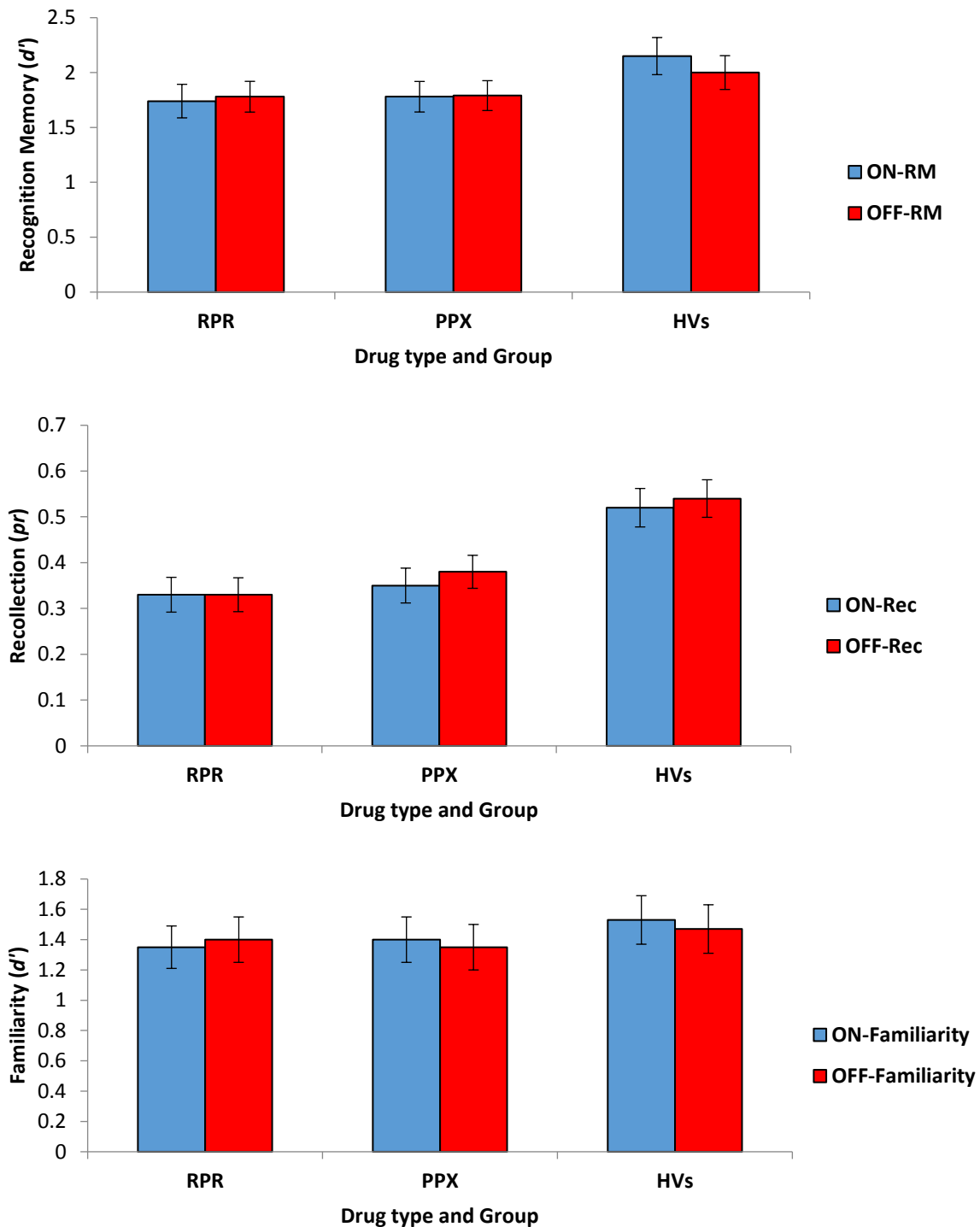


Figure 13. Estimates of recognition memory (top), familiarity (middle), recollection (bottom) and for both ON-medication/Green and OFF-medication Blue conditions by participant group. *Notes and abbreviations.* Error bars represent the standard error of the mean. HVs, Healthy volunteers; ON, medicated; OFF, unmedicated; RM, recognition memory; Rec, Recollection; RPR, Ropinirole; PPX, Pramipexole.

In summary, RM performance was poorer in the PD patients compared to HVs when ON ropinirole and ON pramipexole, but comparable OFF both drugs. Familiarity was comparable to the HVs ON and OFF both ropinirole and pramipexole. Recollection in the PD was significantly impaired to the HVs, in all condition ON and OFF ropinirole, ON and OFF pramipexole). No significant difference emerged between the ON and OFF conditions of ropinirole or pramipexole, however there was a trend for recollection to be poorer in the ON-medication condition compared to the OFF-medication. The familiarity and recollection findings suggest that the RM impairment is attributable to recollection decline and not familiarity.

4.3.2.1. Measures of executive functioning and logical memory

The mean scores and standard deviations for digit span (forwards, reverse and total), Test of Everyday Attention (low demand and high demand), Hayling task (Initiation, suppression, total and scaled score) and logical memory measures (immediate recall, delayed recall and recognition) are presented in Table 15 below. To compare the effect of ropinirole and pramipexole in the whole PD cohort, estimates of these measures were analysed separately using a series of 2 X 2 ANOVAs with two within groups factors Drug (ropinirole vs. pramipexole) and Medicated State (ON-medication vs. OFF-medication). Following these analyses, independent t-tests were used to compare PD group with HVs, across Drug and Medicated State conditions.

Table 15.

Means and standard deviations for logical memory and executive measures for the whole PD cohort on both pramipexole and ropinirole in ON-medication/Green and OFF-medication/Blue conditions.

	Patient Group (n = 16)				Healthy Volunteers (n = 13)	
	Pramipexole		Ropinirole			
	Means (SDs)		Means (SDs)		Means (SDs)	
	ON-medication	OFF-medication	ON-medication	OFF-medication	ON/Green	OFF/BLUE
Digit Span						
Forward	10.63 (2.70)	10.38 (2.28)	10.00 (2.20)	10.56 (2.19)	10.78 (1.64)	11.31 (2.02)
Reverse	7.00 (2.16)	7.06 (1.91)	7.81 (2.37)	7.13 (2.24)	9.31 (1.75)	9.23 (1.83)
Total	17.63 (4.62)	17.44 (3.61)	17.75 (4.25)	17.69 (4.14)	20.08 (3.23)	20.54 (3.64)
Attention						
Low Demand	6.69 (1.01)	6.69 (.48)	6.38 (1.09)	6.25 (1.06)	7.00 (00)	7.00 (00)
High Demand	6.37 (2.53)	7.00 (2.48)	7.00 (2.42)	7.19 (2.31)	7.5 (3.12)	9.25 (.96)
Hayling						
Initiation	6.00 (.52)	6.00 (.73)	5.63 (.96)	5.56 (1.26)	5.25 (.50)	5.5 (.57)
Suppression	12.56 (1.36)	12.38 (2.80)	12.94 (1.29)	12.56(1.06)	13.00 (.82)	11.5 (2.52)
Total Score	18.56 (1.50)	18.38 (2.94)	18.56 (1.75)	18.13 (2.96)	18.25 (.96)	17.00 (2.71)
Scaled Score	6.25 (.77)	6.25 (1.65)	6.5 (1.26)	6.19 (1.51)	6.00 (0.00)	5.50 (1.00)
Logical Memory						
Immediate Recall	25.94 (6.50)	27.75 (7.15)	26.56 (7.66)	26.31(7.95)	37.69 (9.44)	39.39 (9.23)
Delayed Recall	22.13 (5.52)	25.94 (8.71)	21.75 (28.23)	23.44 (8.15)	28.15 (5.97)	28.85 (5.90)
Recognition	25.31 (2.27)	26.00 (2.71)	25.56 (2.80)	25.69 (2.06)	27.38 (1.66)	27.77 (1.54)

Notes and abbreviations. PD, Parkinson's Disease; SD, Standard deviation.

4.3.2.2. Working memory (digit span forwards, reverse and total)

For digit span forwards, there were no significant effects of Drug ($F(1,15), = .15, p = .71$), Medicated State ($F(1,15), = .19, p = .67$). The Drug*Medicated state interaction was also not significant ($F(1,15), = .98, p = .34$). Digit span forwards was comparable to HVs when medicated with ropinirole, in the ON-medication condition ($t(27), -.82, p = .42$), OFF-medication condition ($t(27), = -.85, p = .40$), when medicated with pramipexole in the ON-medication condition ($t(27), = -.09, p = .93$) and in the OFF-medication condition ($t(27), = -1.04, p = .31$).

No significant effects were found for digit span reverse within the PD patients, Drug ($F(1,15), = 1.45, p = .25$), Medicated State ($F(1,15), = 1.39, p = .26$) and the Drug*Medicated State interaction ($F(1,15), = 1.74, p = .21$). When the patients were medicated with ropinirole, in the ON-medication condition, digit span reverse performance was comparable to the HVs ($t(27), = -1.49, p = .15$), however in the OFF-medication condition PD patient were significantly impaired ($t(27), = -3.04, p = .005$). The PD patients were also impaired on the digit span when medicated with pramipexole in the ON-medication condition ($t(27), = -2.68, p = .01$) and OFF-medication condition ($t(27), = -3.09, p = .005$).

For digit span total (forwards plus reverse) no significant effects were found for Drug ($F(1,15), = .31, p = .59$), Medicated State ($F(1,15), = .06, p = .82$) and the Drug*Medicated State was also not significant ($F(1,15), = .01, p = .95$). When medicated with ropinirole, in the ON-medication condition, the PD patient's total digit span performance was comparable to HVs ($t(27), = -1.28, p = .21$) but were borderline significantly impaired when in the OFF-medication condition ($t(27), = -2.01, p = .06$). When medicated with pramipexole the PD patients digit span total performance was comparable to HVs ($t(27), = -1.39, p = .18$), but they were significantly impaired in the OFF-medication condition ($t(27), -2.20, p = .04$).

4.3.2.3. Test of Everyday Attention

For low demand attention, there was no significant effect of Drug ($F(1,15) = .23, p = .64$), Medicated State ($F(1,15) = 2.72, p = .12$), and the Drug*Medicated state interaction was not significant ($F(1,15) = .68, p = .42$). The low demand attention performance of the PD patients was comparable to HVs, when medicated with ropinirole in the ON-medication condition ($t(27) = -1.01, p = .33$), the OFF-medication condition ($t(27) = -1.38, p = .18$), and when medicated with pramipexole, in the ON-medication condition ($t(27) = -.72, p = .48$) and OFF-medication condition ($t(27) = -1.47, p = .16$).

On the high demand attention task, there were no significant effects of Drug ($F(1,15) = 1.12, p = .31$) or Medicated State ($F(1,15) = .41, p = .53$) and the Drug*Medicated State was also not significant ($F(1,15) = .32, p = .59$). PD patient performance was comparable to the HVs when, medicated with ropinirole in the ON-medication condition ($t(27) = -.56, p = .58$) but were borderline significantly impaired in OFF-medication condition ($t(27) = -2.03, p = .06$). When medicated with pramipexole the PD patients were comparable to HVs in the ON-medication condition ($t(27) = -.90, p = .16$), but were borderline significantly impaired in the OFF-medication condition ($t(27) = -1.96, p = .07$).

4.3.2.4. Hayling sentence completion/suppression task

For the initiation task, there was no significant effect of Drug ($F(1,15) = .05, p = .84$), Medicated State ($F(1,15) = 2.71, p = .12$) and the Drug*Medicated State interaction was not significant ($F(1,15) = .07, p = .79$). The Hayling sentence completion task performance in the PD patients was comparable to HVs when medicated with ropinirole in the ON-medication condition ($t(27) = .75, p = .46$) and OFF-medication condition ($t(27) = .10, p = .93$). However the PD patients were significantly impaired when medicated with pramipexole, in the ON-medication condition ($t(27) = 2.61, p = .02$), but not in the OFF-medication condition ($t(27) = 1.27, p = .22$).

For the suppression task, there was no significant main effect of Drug ($F(1,15) = .22, p = .64$), Medicated State ($F(1,15) = 1.41, p = .25$) and the Drug*Medicated State interaction was not significant ($F(1,15) = .17, p = .69$). PD patient performance on the suppression task was comparable to the HVs when patients were medicated with ropinirole in the ON-medication condition ($F(1,15) = -.09, p = .93$), the OFF-medication condition ($F(1,15) = .89, p = .39$), when medicated with pramipexole in the ON-medication ($t(27) = -.61, p = .55$) and OFF-medication ($t(27) = .58, p = .88$) conditions.

For the total Hayling score (initiation and suppression scores combined), there were no significant effects of Drug ($F(1,15) = .19, p = .67$) or Medicated State ($F(1,15) = .79, p = .67$) and the Drug*Medicated State interaction was not significant ($F(1,15) = .33, p = .57$). No significant differences were found between the HVs and the PD patients when medicated with ropinirole, in the ON-medication condition ($t(27) = .34, p = .74$), OFF-medication condition ($t(27) = .69, p = .50$), or when medicated with pramipexole, in the ON-medication condition ($t(27) = .39, p = .70$) and OFF-medication condition ($t(27) = .85, p = .41$).

4.3.2.5. Logical Memory (immediate recall, delayed recall and recognition)

For immediate recall, there were no significant effects of Drug ($F(1,15) = .33, p = .57$), Medicated State ($F(1,15) = .57, p = .46$) and the Drug*Medicated State interaction was also not significant ($F(1,15) = .77, p = .39$). Immediate recall was significantly impaired in relation to the HVs when the PD patients were medicated with ropinirole, in the ON-medication condition ($t(27) = -4.10, p < .001$) and OFF-medication condition ($t(27) = -4.84, p < .001$) and when medicated with pramipexole, in the ON-medication condition ($t(27) = -4.09, p < .001$) and OFF-medication condition ($t(27) = -4.08, p < .001$).

For delayed recall, there was a significant effect of Drug ($F(1,15) = 5.96, p = .03$). This delayed recall decline in both the ON-medication condition when medicated with ropinirole and in

the ON-medication condition when medicated with pramipexole was explored further using pairwise comparisons with a Bonferroni correction control for type 1 error. Analysis did not reveal any significant difference in any of the comparisons; when medicated with ropinirole ON-medication vs. OFF-medication ($p = .10$), when medicated with pramipexole ON-medication vs. OFF-medication ($p = .10$); The ON-medication condition of ropinirole and pramipexole ($p = .69$), or the OFF-medication conditions of both ropinirole and pramipexole ($p = .29$). There was not a significant main effect of Medicated State ($F(1,15) = 1.00, p = .33$) or the Drug*Medicated State interaction ($F(1,15) = .45, p = .52$). Delayed recall was significantly impaired in the PD patients when they were medicated with ropinirole in the ON-medication condition ($t(27) = -3.20, p = .003$) and OFF-medication condition ($t(27) = -2.48, p = .02$), and when medicated with pramipexole in the ON-medication condition ($t(27) = -.06, p = .005$) but not in the OFF-medication condition ($t(27) = -1.37, p = .18$).

For the logical memory recognition task, there was no significant effect of Drug ($F(1,15) = .50, p = .49$) or Medicated State ($F(1,15) = .27, p = .61$) and the Drug*Medicated State interaction was not significant ($F(1,15) = .11, p = .75$). Recognition was impaired in the PD cohort in contrast to HVs across both drugs and conditions; medicated with ropinirole ON-medication ($t(27) = -2.28, p = .03$), OFF-medication ($F(1,15) = -3.22, p = .003$).

In the third set of analysis, to test for a phenotype*drug interaction, whereby by a particular phenotype maybe vulnerable to a drug specific deficit, the PD cohort is divided by phenotype (RPR and PPX) and data is reported from each PD phenotype tested ON and OFF each study drug (ropinirole and pramipexole).

4.3.3. Scenario 3 - a phenotype *drug interaction

The raw hit and false alarm means and standard deviations for RM, *know* and *remember* responses from the PD subgroups (PD group split by phenotype, RPR and PPX), on each drug (ropinirole and pramipexole) from the ON-Medication and OFF-Medication conditions are presented in table 16. Estimates of RM (d'), familiarity (d') and recollection (pr) are presented in Figure 14.

Table 16.

The raw hit and false alarms for Recognition memory, know and remember data, presented for both the ropinirole and pramipexole phenotypes, on both ropinirole and pramipexole across the ON-medication and OFF-medication conditions.

	PD Patient Group (n = 16)							
	Pramipexole Phenotype (n = 7)				Ropinirole Phenotype(n = 9)			
	Pramipexole Means (SDs)		Ropinirole Means (SDs)		Pramipexole Means (SDs)		Ropinirole Mean (SDs)	
	ON-medication	OFF-medication	ON-medication	OFF-medication	ON-medication	OFF-medication	ON-medication	OFF-medication
Recognition memory								
Hits	34.00 (7.93)	32.44 (8.97)	24.43 (11.03)	24.86 (9.03)	35.22 (7.56)	33.44 (9.68)	31.44 (9.38)	29.81 (8.85)
False Alarms	5.56 (4.27)	5.00 (3.95)	5.71 (4.64)	3.57 (2.70)	5.11 (4.78)	3.56 (3.09)	2.25 (4.49)	3.63 (2.90)
<i>d'</i>	1.80 (.54)	1.86 (.59)	1.28 (.57)	1.47 (.42)	1.88 (.64)	2.03 (.61)	1.65 (.64)	1.77 (.59)
Know								
Hits	14.69 (8.57)	10.88 (5.54)	9.71 (6.26)	8.14 (6.20)	13.89 (6.95)	10.78 (4.15)	12.56 (5.67)	11.12 (6.75)
False Alarms	4.25 (3.92)	2.87 (2.39)	3.57 (2.76)	1.43 (1.90)	3.67 (4.27)	2.11 (1.96)	3.12 (2.42)	1.81 (2.07)
<i>d'</i>	1.40 (.54)	1.44 (.67)	.89 (.38)	1.17 (.37)	1.53 (.59)	1.56 (.64)	1.26 (.51)	1.44 (.54)
Remember								
Hits	19.31 (7.92)	21.56 (7.86)	14.71 (8.3)	16.71 (7.91)	21.33 (8.53)	22.67 (8.66)	18.88 (7.94)	18.69 (8.01)
False Alarms	1.31 (.95)	2.13 (2.31)	2.14 (2.79)	2.14 (1.21)	1.44 (.88)	1.44 (1.42)	2.12 (2.60)	1.81 (1.51)
<i>pr</i>	.36 (.15)	.39 (.15)	.25 (.17)	.28 (.15)	.39 (.17)	.42 (.16)	.32 (.17)	.33 (.15)

Notes and abbreviations. PD, Parkinson's Disease; SD, Standard Deviation; *d'*, signal detection measure of discrimination accuracy; *pr*, threshold measure; HV data are presented in previous tables.

To explore the relationship between the PD phenotype and drug type, a series of mixed 2 X 2 X 2 ANOVAs were conducted with a between groups factor of PD Phenotype (RPR vs. PPX) and two within groups factors; Drug (ropinirole vs. pramipexole) and Medicated State (ON-medication vs. OFF-medication). A series of between groups *t*-tests were then used to independently compare each PD phenotypes with HV performance.

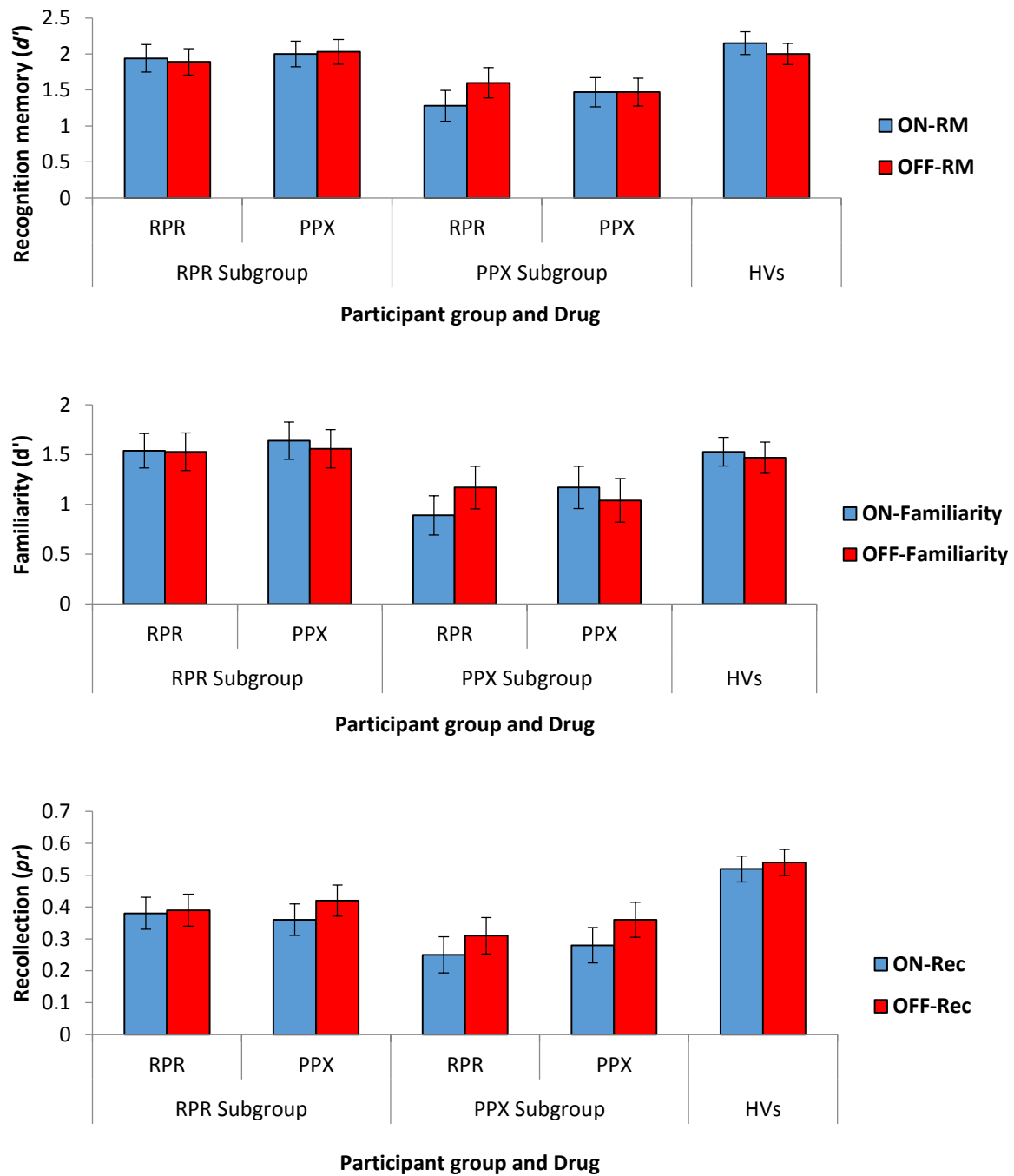


Figure 14. Estimates of recognition memory (top), familiarity (middle), and recollection (bottom) for both ON-Medication/Green and OFF-Medication/Blue conditions by participant group. *Notes and Abbreviations.* Error bars represent the standard error of the mean. HVs, Healthy volunteers; ON, medicated; OFF, unmedicated; RM, recognition memory; Rec, Recollection; RPR, Ropinirole; PPX, Pramipexole.

Analysis of recognition memory estimates revealed a significant effect of phenotype ($F(1,14) = 6.03, p = .03$), further exploration of this effect using pairwise comparisons, revealed that the PPX

phenotype were significantly impaired in contrast to the RPR phenotype when medication with ropinirole in the ON-medication condition ($p = .03$), but were comparable in the OFF-medication condition ($p = .07$). Recognition memory was comparable between the PD phenotypes when medicated with pramipexole, ON-medication ($p = .31$), however, the PPX phenotype were significantly impaired in the OFF-medication condition ($p = .04$). There were no significant effects of Drug ($F(1,14) = .61, p = .45$), or Medicated State ($F(1,14) = .57, p = .46$). No significant interactions were found for Phenotype*Drug ($F(1,14) = .88, p = .37$), Phenotype*Medicated State ($F(1,14) = .17, p = .68$), Drug*Medicated State ($F(1,14) = .29, p = .60$) or Phenotype*Drug*Medicated State ($F(1,14) = .93, p = .35$).

In the RPR phenotype overall recognition memory was comparable in relation to the HVs performance when medicated with ropinirole in the ON-medication ($t(20) = -.85, p = .41$) and OFF-medication conditions ($t(20) = .03, p = .98$), and similarly comparable when medicated with pramipexole in both the ON-medication ($t(20) = -1.03, p = .32$) and OFF-medication condition ($t(20) = .15, p = .88$). In contrast, in the PPX phenotype, recognition memory was significantly impaired compared to HVs in all conditions; when medicated with ropinirole in the ON-medication ($t(20) = -3.24, p = .005$) and OFF-medication ($t(20) = -2.24, p = .04$) condition, and when medicated with pramipexole, ON-medication ($t(20) = -2.31, p = .03$) and OFF-medication ($t(20) = -2.42, p = .03$).

Analysis of familiarity estimates revealed a significant main effect of Phenotype ($F(1,14) = 6.26, p = .03$). Pairwise comparisons used to explore this further showed that the PPX phenotype were significantly impaired in contrast to the RPR phenotype, when medicated with ropinirole in the ON-medication condition ($p = .006$), and OFF-medication; but when medicated with pramipexole the PPX and RPR phenotypes were comparable in the ON-medication condition ($p = .18$), but when OFF-medication the PPX phenotype familiarity impairment approach significance ($p = .07$).

There was no significant main effect of Drug ($F(1,14) = .032, p = .86$) or Medicated state ($F(1,14) = .70, p = .42$). The interactions between Phenotype*Drug ($F(1,14) = .59, p = .46$),

Phenotype*Medicated State ($F(1,14) = .002, p = .96$), Drug*Medicated State ($F(1,14) = 2.17, p = .16$) and Phenotype*Drug*Medicated ($F(1,14) = 1.20, p = .29$) failed to reach significance.

In the RPR phenotype, familiarity performance was comparable to HVs when medicated with ropinirole in the ON-medication ($t(20) = .06, p = .95$) and OFF-medication ($t(20) = .64, p = .53$) conditions. When medicated with pramipexole, familiarity estimates were again comparable to HVs in the ON-medication ($t(20) = .002, p = .99$) and OFF-medication ($t(20) = .34, p = .74$) conditions. For the PPX phenotype, familiarity was significantly impaired when medicated with ropinirole in the ON-medication ($t(18) = -2.43, p = .03$) but not in the OFF-medication condition ($t(18) = -1.13, p = .28$). When medicated with pramipexole familiarity was comparable to HVs in the ON-medication ($t(18) = -1.37, p = .19$) and OFF-medication ($t(18) = -1.69, p = .11$) conditions.

For recollection estimates there was no significant main effect of Phenotype ($F(1, 14) = 1.73, p = .21$). Similarly, analysis revealed no significant main effect of Drug ($F(1,14) = 2.90, p = .11$) or Medicated State ($F(1,14) = 1.82, p = .20$). Furthermore, none of the interactions were significant Phenotype*Drug ($F(1,14) = .32, p = .58$), Phenotype*Medicated State ($F(1,14) = 1.05, p = .32$), Drug*Medicated State ($F(1,14) = .24, p = .64$) and Phenotype*Drug*Medicated State ($F(1,14) = .09, p = .77$).

A series of between groups *t*-tests were used to explore the differences between the RPR and PPX phenotype patients and the HVs. For the RPR phenotype patients, when medicated with ropinirole, recollection was significantly impaired compared to the HVs in the ON-medication condition ($t(20) = -2.28, p = .03$, and in the OFF-medication condition ($t(20) = -2.88, p = .009$). However when the RPR phenotype were medicated with pramipexole, recollection estimates only approached significance compared to controls both ON-medication ($t(20) = -1.93, p = .07$) and OFF-medication ($t(20) = -1.95, p = .07$).

Recollection estimates for the PPX phenotype patients were significantly impaired in contrast to HVs in all conditions, when medicated with Ropinirole, ON-medication, ($t(18) = -3.75, p < .001$),

OFF-medication ($t(18)$, = -3.80, $p < .001$) and when medicated with pramipexole ON-medication ($t(18)$, = -3.10, $p = .006$) and OFF-medication ($t(18)$, = -2.23, $p = .01$).

To summarise these findings, overall recognition memory performance in the RPR phenotype was comparable to HVs ON and OFF ropinirole and pramipexole. The PPX phenotype, were significantly impaired to HVs ON and OFF ropinirole and pramipexole. They were also impaired compared to the RPR phenotype, but only when ON and OFF ropinirole.

In the PPX phenotype, familiarity was significantly impaired compared to the RPR phenotype ON and OFF ropinirole, but not pramipexole. Familiarity was preserved in the RPR phenotype, compared to HVs in both the ON and OFF conditions of both ropinirole and pramipexole, whereas in the PPX phenotype, familiarity was significantly poorer than HVs, but only when medicated with ropinirole.

There were no significant differences in the recollection performance of the 2 PD phenotypes, on either ON or OFF pramipexole or recollection. The RPR phenotype were significantly impaired in contrast to HVs, ON and OFF ropinirole but were comparable to controls ON and OFF pramipexole. Whereas the PPX phenotype showed a significant recollection decline in contrast to HVs, ON and OFF both ropinirole and pramipexole.

4.3.3.1. Measures of executive function and logical memory

The means and standard deviation for digit span (forwards, reverse and total), Test of Everyday Attention (low demand and high demand), Hayling task (Initiation, suppression, and total score) and logical memory measures (immediate recall, delayed recall and recognition) are presented in Table 17 below. To explore the effect PD phenotype by drug (ropinirole and pramipexole), estimates of these measures were analysed separately using a series of 2 X 2 X 2 ANOVAs with a between groups factor whereby the PD patients are divided by Phenotype (RPR vs. PPX) and two within groups factors Drug (ropinirole vs. pramipexole) and Medicated State (ON-medication vs. OFF-medication). Following

these analyses, independent *t*-tests were used to compare phenotypes with HVs, across Drug and Medicated State conditions.

Table 17.

Means and standard deviations for logical memory and executive measures for the PPX and RPR phenotypes on both pramipexole and ropinirole in ON-medication and OFF-medication conditions.

	PD Patient Group (n = 16)							
	PPX phenotype (n = 7)				RPR Phenotype (n = 9)			
	Pramipexole Means (SDs)		Ropinirole Means (SDs)		Pramipexole Means (SDs)		Ropinirole Means (SDs)	
	ON-medication	OFF-medication	ON-medication	OFF-medication	ON-medication	OFF-medication	ON-medication	OFF-medication
Hoehn and Yahr	2.29 (.57)	2.43 (.53)	2.21 (.64)	2.43 (.53)	2.00 (.71)	2.17 (.50)	2.11 (.49)	2.17 (.43)
UPDRS	12.29 (4.61)	11.86 (2.54)	12.57 (3.41)	14.00 (3.92)	11.11 (5.71)	12.33 (4.03)	11.56 (4.61)	13.00 (4.12)
Epworth	8.29 (6.26)	-	8.14 (6.26)	-	12.33 (5.20)	-	9.56 (3.97)	-
Apathy	12.00 (5.63)	8.67 (3.32)	12.14 (5.52)	14.00 (8.53)	12.75 (7.49)	16.25 (8.85)	13.71 (9.66)	14.75 (11.67)
Digit Span								
Forward	9.71 (2.92)	10.29 (2.69)	9.57 (2.64)	9.71 (1.98)	11.44 (2.55)	10.56 (2.29)	10.56 (2.30)	11.33 (2.29)
Reverse	7.14 (2.61)	6.86 (1.95)	7.57 (3.51)	6.71 (1.70)	7.22 (2.33)	7.22 (1.97)	8.33 (2.12)	7.22 (2.39)
Total	16.86 (5.49)	17.14 (4.53)	17.00 (6.14)	16.43 (3.60)	18.67 (4.58)	17.78 (3.27)	18.89 (3.82)	18.56 (4.36)
Attention								
Low Demand	6.29 (1.50)	6.71 (.48)	6.14 (1.57)	6.14 (1.21)	6.89 (.33)	6.56 (.53)	6.67 (.50)	6.33 (1.00)
High Demand	6.29 (3.09)	7.00 (2.83)	6.43 (1.81)	7.00 (2.45)	6.00 (2.45)	6.44 (2.40)	6.89 (2.98)	6.67 (2.34)
Hayling								
Initiation	6.00 (.58)	5.71 (.76)	5.29 (.95)	5.00 (1.15)	6.00 (.50)	6.22 (.67)	5.89 (.93)	6.00 (1.22)
Suppression	12.00 (1.41)	11.71 (2.69)	12.14 (.69)	12.14 (1.95)	13.00 (1.22)	12.89 (2.93)	13.56 (1.33)	12.89 (2.20)
Total Score	18.00 (1.53)	17.43 (2.51)	17.42 (.98)	17.14 (2.97)	19.00 (1.41)	19.11 (3.18)	19.44 (1.74)	18.89 (2.89)
Scaled Score	5.86 (.38)	5.57 (1.13)	5.86 (.38)	5.71 (1.25)	6.56 (.88)	6.78 (1.86)	7.00 (1.50)	6.56 (1.67)
Logical Memory								
Immediate Recall	25.00 (5.69)	25.43 (3.31)	24.86 (5.30)	26.29 (6.90)	26.00 (7.35)	28.33 (8.97)	26.11 (7.51)	24.67 (6.14)
Delayed Recall	21.42 (7.81)	21.43 (5.47)	20.43 (5.32)	20.86 (7.69)	21.11 (4.94)	27.67 (10.11)	20.67 (6.14)	24.00 (7.14)
Recognition	25.57 (2.44)	25.43 (1.51)	25.43 (2.23)	26.14 (1.68)	25.44 (2.13)	26.33 (3.39)	25.44 (3.13)	25.22 (2.17)

Notes and abbreviations. PD, Parkinson's Disease; PPX, Pramipexole; RPR, Ropinirole; SD, Standard Deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

4.3.3.2. Working memory (digit span forwards, reverse and total)

For digit Span forwards there was no significant main effect of Phenotype ($F(1,14)$, = 1.21, p = .29), Drug ($F(1,14)$, = .22, p = .65), Medicated State ($F(1,14)$, = .20, p = .66). None of the interactions were significant; Drug*Phenotype ($F(1,14)$, = .12, p = .74), Medicated State*Phenotype ($F(1,14)$, = .67, p = .55), Drug*Medicated State ($F(1,14)$, = .71, p = .42) and Drug*Medicated State*Phenotype ($F(1,14)$, = 2.02, p = .18).

In the RPR phenotype, digit span forwards performance was comparable to HVs when medicated with ropinirole both in the ON-medication ($t(20)$, = -.26, p = .80) the OFF-medication condition ($t(20)$, = .03, p = .98). Similarly, when the RPR phenotype, were medicated with pramipexole, performance on the digit span forwards task was not significantly different from the HV, in the ON-medication ($t(20)$, = .76, p = .46) or the OFF-medication condition ($t(20)$, = -.81, p = .43). No significant differences emerged between the HVs and the PPX phenotype, when medicated with ropinirole in the ON-medication condition ($t(18)$, = -1.26, p = .22), however the PPX were significantly impaired in the OFF-medication condition ($t(18)$, -3.00, p = .008). When medicated with pramipexole, the PPX phenotype were not significantly impaired in either the ON-medication ($t(18)$, = -1.04, p = .31) or OFF-medication conditions ($t(18)$, = -.96, p = .35),

For digit span reverse, there were no significant main effects of Phenotype ($F(1,14)$, = .19, p = .67), Drug ($F(1,14)$, = 1.14, p = .30), Medicated State ($F(1,14)$, = 1.34, p = .27). Interactions were also not significant Drug*Phenotype ($F(1,14)$, = .40, p = .54), Medicated State*Phenotype ($F(1,14)$, = .00, p = .99), Drug*Medicated State ($F(1,14)$, = 1.49, p = .24) and Drug*Medicated State*Phenotype ($F(1,14)$, = .15, p = .70).

In the RPR phenotype, when medicated with ropinirole, digit span reverse performance was comparable to HVs when ON-medication ($t(20)$, = -1.18, p = .25), but were impaired when OFF-medication ($t(20)$, = -2.24, p = .04). When medicated with pramipexole, the RPR phenotype were significantly impaired when ON-medication ($t(20)$, = -2.40, p = .03) and OFF-medication ($t(20)$, = -

2.44, $p = .02$). The PPX phenotype, when medicated with ropinirole, were comparable to HVs when in the ON-medication condition ($t(18) = -1.50$, $p = .15$), but were significantly impaired when in the OFF-medication condition ($t(18) = -3.00$, $p = .008$). Digit span reverse was also impaired compared to HVs when the PPX phenotype were medicated with pramipexole in the ON-medication ($t(18) = -2.22$, $p = .04$) and OFF-medication ($t(18) = -2.70$, $p = .02$) conditions.

For digit span total (forwards plus reverse), there were no significant main effects of Phenotype ($F(1,14) = .68$, $p = .43$), Drug ($F(1,14) = .03$, $p = .88$) or Medicated State ($F(1,14) = .68$, $p = .43$). There were also no significant interactions between Drug*Phenotype ($F(1,14) = .33$, $p = .57$), Medicated State*Phenotype ($F(1,14) = .10$, $p = .76$), Drug*Medicated State ($F(1,14) = .03$, $p = .88$) and Drug*Medicated State*Phenotype ($F(1,14) = .55$, $p = .47$).

The RPR phenotype were comparable to HVs, when medicated with ropinirole in the ON-medication ($t(20) = -.79$, $p = .44$) and OFF-medications ($t(23) = -1.16$, $p = .26$). Similarly, when medicated with pramipexole, the RPR phenotype digit span total scores were consistent with HVs ON-medication ($t(20) = -.85$, $p = .41$) and OFF-medication ($t(20) = -1.82$, $p = .08$). In the PPX phenotype, when medicated with ropinirole, were comparable in the ON-medication condition ($t(18) = -1.49$, $p = .15$), but were impaired OFF-medication ($t(18) = -2.42$, $p = .03$). Similarly, the PPX phenotype, were comparable to HVs when medicated with pramipexole in the ON-medication condition ($t(18) = -1.67$, $p = .10$), but approached significant impairment when OFF-medication ($t(18) = -1.83$, $p = .08$).

4.3.3.3. Test of Everyday Attention

For the low demand attention task, there were no significant main effects of Phenotype ($F(1,14) = .55$, $p = .47$), Drug ($F(1,14) = 2.68$, $p = .12$) or Medicated State ($F(1,14) = .10$, $p = .76$). Also, there were significant interactions for Drug*Phenotype ($F(1,14) = .15$, $p = .71$), Medicated State*Phenotype ($F(1,14) = 2.09$, $p = .17$), Drug*Medicated State ($F(1,14) = .86$, $p = .37$) or Drug*Medicated State*Phenotype ($F(1,14) = .86$, $p = .37$).

In the RPR phenotype, when medicated with ropinirole performance on the low demand attention task was consistent with HVs in the ON-medication ($t(20) = -1.30, p = .22$) and OFF-medication ($t(20) = -1.30, p = .22$). When medicated with pramipexole the no significant differences emerged in either the ON-medication ($t(20) = -.65, p = .53$) or OFF-medication ($t(20) = -1.65, p = .13$). For the PPX phenotype performance on the low demand attention task was consistent with HVs when medicated with ropinirole ON-medication ($t(18) = -1.06, p = .32$) and OFF-medication ($t(18) = -1.38, p = .20$), and when medicated with pramipexole, ON-medication ($t(18) = -.93, p = .38$) and OFF-medication ($t(18) = -1.14, p = .28$).

For the high demand attention task, there were no significant effects of Phenotype ($F(1,14) = .03, p = .87$), Drug ($F(1,14) = .32, p = .58$) or Medicated State ($F(1,14) = 1.29, p = .28$). There were no significant interactions for Drug*Phenotype ($F(1,14) = .19, p = .67$), Medicated State ($F(1,14) = 1.29, p = .28$), Drug*Medicated State ($F(1,14) = .24, p = .63$) or Drug*Medicated State*Phenotype ($F(1,14) = .10, p = .76$).

For the RPR phenotype, high demand attention was comparable to HVs when medicated with ropinirole in the ON-medication ($t(20) = -.34, p = .74$) but approached a significant deficit in the OFF-medication condition ($t(20) = -2.09, p = .06$). Similarly, when medicated with pramipexole, the RPR phenotype were consistent with HVs ON-medication ($t(20) = -.94, p = .37$), but were significantly impaired when OFF-medication ($t(20) = -2.21, p = .05$). In the PPX phenotype, when medicated with ropinirole, performance on the high demand attention task was consistent with HVs, both ON-medication ($t(18) = -.74, p = .48$) and OFF-medication ($t(18) = -1.73, p = .12$). Similarly, the PPX phenotype were consistent with the HVs when medicated with pramipexole in the ON-medication ($t(18) = -.63, p = .55$) and OFF-medication ($t(18) = -1.51, p = .17$) conditions.

4.3.3.4. Hayling sentence completion and suppression task

For the initiation task, there were no significant main effects for Phenotype ($F(1,14)$, = 2.76, p = .12), Drug ($F(1,15)$, = 3.19, p = .10) or Medicated State ($F(1,14)$, = .18, p = .69). There were no significant interactions between Drug*Phenotype ($F(1, 14)$, = 1.23, p = .29), Medicated State*Phenotype ($F(1,14)$, = 2.55, p = .13), Drug*Medicated State ($F(1,14)$, = .05, p = .82) or Drug*Medicated State*Phenotype ($F(1,14)$, = .05, p = .82).

For the RPR phenotype, when medicated with ropinirole, performed consistently with the HVs, in the ON-medication ($t(20)$, = 1.28, p = .23) and OFF-medication ($t(20)$, = .77, p = .46). When medicated with pramipexole, the RPR phenotype were significantly impaired in the ON-medication ($t(20)$, = 2.50, p = .03 in contrast to HVs, but was comparable in the OFF-medication condition ($t(20)$, = 1.87, p = .09). For the PPX phenotype, performance on the Hayling initiation task, when medicated with ropinirole, was comparable to HVs, in the ON-medication ($t(18)$, = .07, p = .95) and OFF-medication condition ($t(18)$, = -.80, p = .45). When the PPX phenotype were medicated with pramipexole, in the ON-medication condition, performance approached a significant impairment compared to HVs ($t(18)$, = 2.17, p = .06), but were comparable when OFF-medication ($t(18)$, = .49, p = .64).

For the suppression task, there were no significant main effects of Phenotype ($F(1,14)$, = 2.48, p = .14), Drug ($F(1,14)$, = 1.30, p = .27) or Medicated State ($F(1,14)$, = .18, p = .68). There were no significant interaction effects between Drug*Phenotype ($F(1,15)$, = .00, p = .99), Medicated State*Phenotype ($F(1,14)$, = .04, p = .85), Drug*Medicated State ($F(1,14)$, = .08, p = .78) or Drug*Medicated State*Phenotype ($F(1,14)$, = .82, p = .38).

For the RPR phenotype, when medication with ropinirole, in the ON-medication condition, performance on the Hayling suppression task was comparable to HVs ($t(20)$, = .76, p = .46) and when OFF-medication ($F(20)$, = 1.01, p = .34). Similarly, when the RPR phenotype were medicated with pramipexole and in the ON-medication condition ($t(20)$, = -1.86, p = .10) and OFF-medication

condition ($t(20)$, = .48, p = .65), performance was comparable to HVs. In the PPX phenotype, when medicated with ropinirole, performance was comparable to HVs in the ON-medication ($t(18)$, = -1.86, p = .10) and OFF-medication ($t(18)$, = .48, p = .65) conditions. When the PPX phenotype were medicated with pramipexole performance was on the Hayling suppression task was comparable to the HVs ON-medication ($t(18)$, = -1.28, p = .23) and OFF-medication ($t(18)$, = .13, p = .90)

For the Hayling total score (initiation plus suppression), there were no significant main effects of Phenotype ($F(1,14)$, = 3.29, p = .09), Drug ($F(1,14)$, = .29, p = .60) or Medicated State ($F(1,14)$, = .25, p = .63). There were no significant interaction effects between Drug*Phenotype ($F(1,14)$, = .84, p = .38), Medicated State*Phenotype ($F(1,14)$, = .03, p = .88), Drug*Medicated State ($F(1,14)$, = .19, p = .67) or Drug*Medicated State*Phenotype ($F(1,14)$, = 1.21, p = .29).

In the RPR phenotype, when medicated with ropinirole total Hayling total score was comparable to HVs in the ON-medication ($t(20)$, = 1.27, p = .23) and OFF-medication ($t(20)$, = 1.11, p = .29) conditions. Similarly, when medicated with pramipexole, the RPR phenotype were comparable to HVs in the ON-medication ($t(20)$, = .96, p = .36) and OFF-medication condition ($t(20)$, = 1.15, p = .28). For the PPX phenotype, when medicated with ropinirole, total Hayling performance was comparable to the HVs when ON-medication ($t(18)$, = -1.35, p = .21) and OFF-medication ($t(18)$, = .08, p = .94). Similarly, when the PPX phenotype were medicated with pramipexole they were comparable to HVs when ON-medication ($t(18)$, = -.29, p = .78) and OFF-medication ($t(18)$, = .27, p = .80).

4.3.3.5. Logical Memory (immediate recall, delayed recall and recognition)

For immediate recall, there was no significant main effects of Phenotype ($F(1,14)$, = .10, p = .76), Medicated State ($F(1,14)$, = .39, p = .54) or Drug ($F(1,14)$, = .34, p = .57). Interactions were not significant between Medicated State *Phenotype, ($F(1,14)$, = .89, p = .36), Drug*Phenotype ($F(1,15)$, = .04, p = .84), Medicated State*Drug ($F(1,14)$, = .53, p = .48) or Medicated State*Drug*Phenotype ($F(1,14)$, = 1.58, p = .23).

In the RPR phenotype, when medicated with ropinirole, immediate recall was significantly impaired in contrast to HVs in the ON-medication condition ($t(20) = -3.06, p = .006$) and OFF-medication ($t(20) = -4.17, p < .001$) condition. When medicated with pramipexole, the RPR phenotype were impaired in relation to the HVs in both the ON-medication ($t(20) = -3.11, p = .006$) and OFF-medication ($t(20) = -2.79, p = .01$). Immediate recall the PPX phenotype, when medicated with ropinirole were significantly impaired compared to HVs in both the ON-medication ($t(18) = -3.30, p = .004$) and OFF-medication ($t(18) = -3.28, p = .004$). When the PPX phenotype were medicated with pramipexole, they were again significantly impaired in relation to the HVs ON-medication ($t(18) = -3.23, p = .005$) and the OFF-medication ($t(18) = -3.83, p = .001$).

For delayed recall, there were no significant main effects of Phenotype ($F(1,14) = .64, p = .44$) or Medicated State ($F(1,14) = .83, p = .38$). There was a significant main effect of Drug ($F(1,14) = 6.00, p = .03$), as was the interaction between Drug*Phenotype ($F(1,14) = 5.04, p = .04$). These two significant effects were further explored using pairwise comparisons with a Bonferroni correction to control for type 1 error. Analysis revealed that delayed recall was significantly impaired in the RPR phenotype when medicated with ropinirole in the ON-medication compared to when medicated with pramipexole in the ON-medication condition. The RPR phenotype were also significantly impaired when medicated with ropinirole in the OFF-medication condition compared to when medicated with pramipexole in the OFF-medication condition. The remaining interaction were not significant, Medicated State*Phenotype ($F(1,14) = .17, p = .69$), Medicated State*Drug ($F(1,14) = .31, p = .58$) and Medicated State*Drug*Phenotype ($F(1,14) = .54, p = .48$).

In the RPR phenotype, when medicated with ropinirole, delayed recall was significantly impaired compared to HVs in the ON-medication ($t(20) = -2.55, p = .02$) but not in the OFF-medication condition ($t(20) = -1.74, p = .10$). When the RPR phenotype were medicated with pramipexole, delayed recall was significantly impaired in relation to HVs in the ON-medication condition ($t(20) = -2.91, p = .009$) but not in the OFF-medication condition ($t(20) = -.35, p = .73$). In

the PPX phenotype, when medicated with ropinirole, delayed recall was significantly impaired compared to HVs in the ON-medication ($t(18), = -2.86, p = .01$) and OFF-medication ($t(18), = -2.60, p = .02$). Similarly, when medicated with pramipexole, the PPX phenotype were significantly impaired in both the ON-medication ($t(18), = -2.16, p = .04$) and OFF-medication ($t(18), = -2.75, p = .01$) conditions.

For the recognition task, there were no significant main effects of Phenotype ($F(1,14), = .001, p = .98$), Medicated State ($F(1,14), = .14, p = .71$) or Drug ($F(1,14), = .45, p = .51$). There were no significant interactions between Medicated State*Phenotype ($F(1,14), = 1.39, p = .26$), Drug*Phenotype ($F(1,14), = .003, p = .96$), Medicated State*Drug ($F(1,14), = .03, p = .87$) or Medicated State*Drug*Phenotype ($F(1,14), = 1.70, p = .21$).

In the RPR phenotype, when medicated with ropinirole, recognition impairment approached significance in relation to HVs in the ON-medication condition ($t(20), = -1.90, p = .07$) and was significant in the OFF-medication condition ($t(20), = -3.24, p = .004$). When the RPR phenotype was medicated with pramipexole, recognition was impaired in the ON-medication condition ($t(18), = -2.40, p = .03$) but was consistent with HVs in the OFF-medication condition ($t(20), = -1.35, p = .19$). In the PPX phenotype, when medicated with ropinirole, recognition was impaired in relation to HVs in both the ON-medication ($t(18), = -2.23, p = .04$) and OFF-medication ($t(18), = -2.19, p = .04$) condition. When medicated with pramipexole, recognition impairment in the PPX phenotype only approached significance in relation to HVs in the ON-medication condition ($t(18), = -1.98, p = .18$), but was significant in the OFF-medication condition ($t(18), = -3.27, p = .004$).

4.3.4. The relationship between recollection, immediate recall and delayed recall

The second aim of this pilot trial was to assess if immediate recall or delayed recall could be used as an alternative measure to recollection. Bivariate, Pearson correlation were calculated and are presented in Table 18. Across conditions, from this pilot trial it appears that recollection correlates with immediate recall in both ON-medication and OFF-medication conditions across both

ropinirole and pramipexole treatment arms. This is not the case for delayed recall. Therefore in the following section, sample size calculations are calculated for immediate recall.

Table 18.

Correlations between recollection, immediate recall and delayed recall.

	ON-Immediate Recall	OFF-Immediate Recall	ON-Delayed Recall	OFF-Delayed Recall
<i>Ropinirole</i>				
ON-Recollection	$r = .47, p = .009$	-	$r = .36, p = .06$	-
OFF-Recollection	-	$r = .48, p = .009$	-	$r = .47, p = .01$
<i>Pramipexole</i>				
ON-Recollection	$r = .48, p = .009$	-	$r = .47, p = .01$	-
OFF-Recollection	-	$r = .37, p = .04$	-	$r = .26, p = .17$

4.3.5. Sample size calculations

4.3.5.1. Recollection as an outcome variable.

The following sample size calculations are conducted with data from the PD patient cohort grouped as a whole ($n = 16$). Estimates are produced using G*Power software. For recollection, a one tailed hypothesis, with an effect size of .37, $\alpha = 0.05$, power = .80 a total sample size of 47 is required to illustrate the differences between patients ON-medication (ropinirole and pramipexole). To specifically investigate the effect of pramipexole on recollection (ON-medication vs. OFF-medication, a one tailed hypothesis, with an effect size of .35, $\alpha = 0.05$, power = .80 a total sample size of 51 would be required.

4.3.5.2. Immediate recall as an outcome variable

For immediate recall, to compare the ON-medication ropinirole with the ON-medication pramipexole performance with a one tailed hypothesis, with an effect size of .21, $\alpha = 0.05$, power = .80 a sample size of 137 PD patients would be required. To specifically investigate the effect of

pramipexole on immediate recall (ON-medication vs. OFF-medication), a one tailed hypothesis, with an effect size of .45, $\alpha = 0.05$, power = .80 a total sample size of 33 would be required.

4.3.6. Combining data from Study 1 and Study 2 (phase 1 only)

To increase the statistical power of the investigation into the comparative effects of ropinirole and pramipexole on recognition memory in PD, data from the measures that were used in both study 1 and study 2 (phase 1 only), were combined. The combined demographic, neuropsychological characteristics from the 2 studies are presented in Table 19 below.

Table 19.

The demographic, neuropsychological and clinical characteristics of Healthy Volunteers and PD patients combined from study 1 and phase 1 of study 2.

	Healthy Volunteers (n = 23)	PD subgroups combined (n= 37)	Ropinirole subgroup (n = 19)	Pramipexole subgroup (n = 18)
Parameter	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	66.00 (5.20)	65.79 (7.01)	65.89 (7.23)	65.68 (1.60)
Sex (F/M)	9/14	13/25	4/19	9/19
MMSE	29.74 (.45)	28.59 (4.86)	29.34 (.94)	27.84 (6.82)
Premorbid IQ (WTAR)	109.65 (4.90)	103.68 (19.10)	107.84 (12.09)	99.53 (23.81)
Somnolence	2.00 (.47)	10.45 (5.04)***	10.12 (4.43)***	10.79 (5.69)***
Hoehn and Yahr Stage				
ON-medication	-	2.39 (.69)	2.42 (.73)	2.37 (.68)
OFF-medication	-	2.59 (.61)	2.61 (.66)	2.58 (.58)
UPDRS				
ON-medication	-	11.89 (5.00)	13.11 (3.49)	10.68 (5.57)
OFF-medication	-	14.37 (4.89)	15.05 (3.49)	13.68 (6.00)

Notes and abbreviations. Significant differences compared to Healthy Volunteers at, **p<.01, ***p<.001; MMSE, Mini Mental Status Examination (Folstein et al., 1975); PD, Parkinson's Disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale (Fahn et al, 1987); WTAR, Wechsler Scale of Adult Reading (Wechsler, 2001).

4.3.6.1 Matching PD patients and HVs

The PD patients (subgroups combined) were matched to HVs for gender, age ($t(59) = .13, p = .90$), premorbid IQ (Wechsler Test Adult Reading, Wechsler, 2001, [WTAR]: $t(59) = 1.47, p = .15$) and current levels of functioning (Mini-Mental Status Examination, Folstein, Folstein & McHugh, 1975 [MMSE]: $t(59) = 1.13, p = .23$), but not for somnolence (sleepiness, Epworth Sleepiness Scale, Johns, 1991 [ESS]: $t(55) = -7.23, p < .001$).

When the PD patients were divided into subgroups on the basis of their existing D2 dopamine agonist, ropinirole (RPR) or pramipexole (PPX), the two subgroups were matched for demographic, neuropsychological and clinical characteristics such as; gender, age ($t(59) = .13, p = .90$), current levels of cognitive functioning (MMSE ($t(36) = .95, p = .35$), premorbid IQ (WTAR ($t(36) = .74, p = .18$) and somnolence (ESS: $t(36) = -.41, p = .68$), disease severity (Hoehn and Yahr (1967) scale [HY], ON-medication: $t(19) = -.23, p = .82$ and OFF-medication: $t(19) = .13, p = .90$); motor subsection of the Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987, [UPDRS] ON-medication: $t(19) = .75, p = .14$) and OFF-medication: $t(19) = .86, p = .40$). Each PD subgroup was also matched to the HVs on gender, age (RPR subgroup: $t(40) = .06, p = .96$; PPX subgroup: $t(40) = .17, p = .87$), premorbid IQ (WTAR, RPR subgroup: $t(40) = .66, p = .52$; PPX subgroup: $t(40) = 1.99, p = .06$), current levels of cognitive functioning (MMSE, RPR subgroup: $t(40) = 1.80, p = .96$; PPX subgroup: $t(19) = 1.34, p = .19$) but not for somnolence (ESS, RPR subgroup: $t(40) = -7.92, p < .001$; PPX subgroup: $t(40) = -6.71, p < .001$).

The RPR and PPX subgroups were matched for dosage on all dopaminergic medication classes l-dopa ($t(36) = .26, p = .79$) equivalent agonist dose ($t(36) = .14, p = .89$), monoamine-oxidase-B-inhibitor ($t(36) = .66, p = .51$) and Equivalent Daily Dopamine Load (Tomlinson et al, 2010; $t(36) = .70, p = .53$). The means and standard deviations of medication dosages per drug class are presented in Table 20.

Table 20.

The means and standard deviations of dopaminergic medication dosages for the PD cohort and divided by agonist; ropinirole and pramipexole subgroups.

	PD subgroups combined (n= 37)	Ropinirole subgroup (n = 19)	Pramipexole subgroup (n = 18)
Drug	Mean (SD)	Mean (SD)	Mean (SD)
L-dopa dose (mg/day)	262.17 (250.95)	273.03 (241.24)	251.32 (266.47)
Agonist dose (mg/day)	5.14 (4.40)	8.26 (4.32)	2.02 (.81)
Agonist Equivalent (mg/day)	8.18 (3.76)	8.26 (4.32)	8.09 (3.23)
Maob-I (mg/day)	2.24 (3.66)	2.63 (3.71)	1.84 (3.66)
LEDD (mg/day)	4.33.31 (292.18)	403.19 (300.56)	463.42 (288.48)

Notes and abbreviations. MaoB-I, Monoamine-oxidase-B-inhibitor; mg, milligrams; LEDD, L-dopa Equivalent Daily Dose (Tomlinson et al., 2010); PD, Parkinson's Disease; SD, standard deviation.

4.3.6.2. Data analysis of PD patients (subgroups combined) compared with HVs

The raw hit and false alarm means and standard deviations for recognition memory, *know* and *remember* responses for the PD group (subgroups combined) and the HVs by ON-medication/Green and OFF-medication/Blue conditions are shown in Table 21.

Table 21.

The means and standard deviations for raw hits, false alarms and total scores for recognition memory, know and remember for the Healthy Volunteers and PD subgroups combined across both ON-medication/Green and OFF-medication/Blue conditions.

	Healthy Volunteers (n = 23)		PD subgroups combined (n = 37)	
	Means (SD)		Means (SD)	
	ON/Green	OFF/Blue	ON-medication	OFF-medication
Recognition memory				
Hits	38.00 (5.85)	37.13 (6.16)	32.08 (7.96)	31.95 (8.35)
False Alarms	3.70 (2.79)	4.26 (3.41)	5.45 (3.75)	4.68 (3.36)
d'	2.20 (.57)	2.09 (.56)	1.67 (.40)	1.77 (.47)
Know				
Hits	9.09 (3.40)	8.04 (3.18)	12.34 (6.35)	10.68 (5.97)
False Alarms	2.52 (2.21)	2.17 (1.75)	3.39 (2.50)	2.68 (2.57)
d'	1.53 (.61)	1.49 (.63)	1.32 (.41)	1.37 (.54)
Remember				
Hits	28.04 (6.32)	29.26 (6.05)	20.13 (1.31)	21.55 (9.00)
False Alarms	1.00 (1.04)	2.08 (2.94)	2.05 (.43)	1.95 (1.86)
Pr	.53 (.14)	.55 (.13)	.35 (.15)	.39 (.56)

Notes and abbreviations. d' , signal detection measure of discrimination accuracy; pr , threshold measure. PD, Parkinson's Disease; SD, Standard Deviation.

With PD patients grouped together, the RM (d'), familiarity (d') and recollection (pr) estimates across ON-medication and OFF-medication conditions were analysed separately using a series of 2 X 2 ANOVAs. The between subjects factor was Group (HV vs. PD group) and the within subjects factor was Condition (ON-medication/Green vs. OFF-Medication/Blue). Significant main effects were analysed further using planned, multiple pairwise comparisons with Bonferroni corrections to control for type 1 error. The mean and standard deviations of RM (d'), familiarity (d') and recollection (pr) estimates are presented in Figure 15.

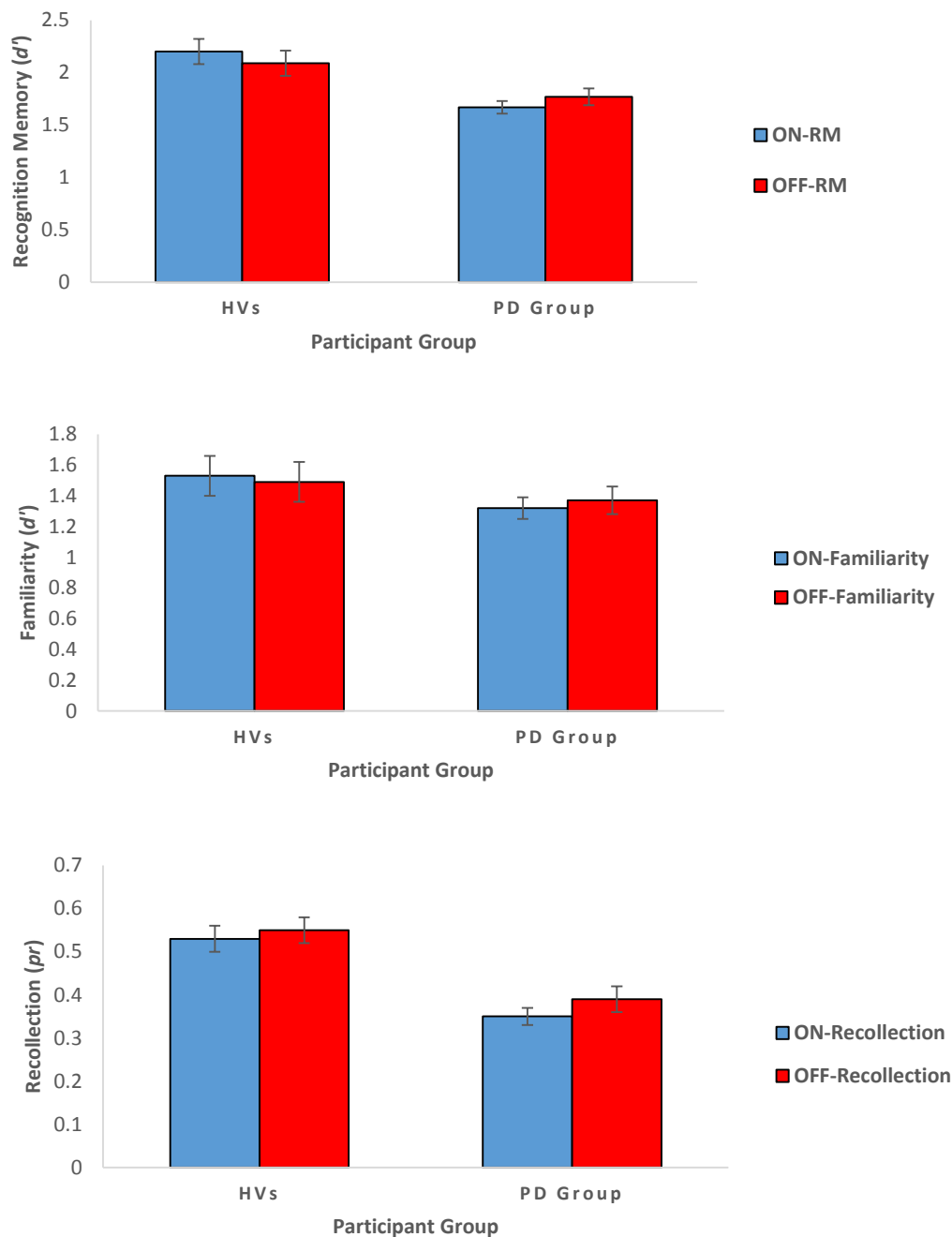


Figure 15. Estimates of recognition memory (top), familiarity (middle), recollection (bottom) and for both ON-medication/Blue and OFF-medication Red conditions by participant group. Error bars represent the standard error of the mean. *Notes and abbreviations.* HVs, Healthy Volunteers; PD, Parkinson's Disease; RM, recognition memory.

Analysis of RM (d') estimates revealed a significant main effect of Group ($F(1,59)$, = 13.84, p < .001). However, there was no significant effect of Condition ($F(1,59)$, = .002, p = .97) and the Interaction was not significant ($F(1,59)$, = 2.83, i = .10). Exploration of the significant effect of Group, using Bonferroni corrected, planned pairwise comparisons showed RM to be significantly impaired in

the PD patients compared to the HVs in both the ON-medication/Green ($p = .02$) and OFF-medication/Blue ($p < .001$) conditions.

A second 2 x 2 ANOVA of familiarity (d') estimates showed no significant main effects of Group ($F(1,59), = 1.83, p = .18$) or Condition ($F(1,59), = .01, p = .91$). Similarly, there was no significant Interaction ($F(1,59), = .37, p = .55$).

Analysis of recollection (pr) estimates revealed a significant main effect of Group ($F(1,59), = 22.29, p < .001$). However, Condition ($F(1,59), = .23, p = .09$) and the Interaction were not significant ($F(1,59), = .23, p = .63$). Further exploration of the main effect of Group with planned, pairwise comparison with a Bonferroni correction, revealed that recollection was significantly impaired in comparison to the HVs in both the ON-medication/Green ($p < .001$) and OFF-medication/Blue ($p < .001$) conditions.

In Summary, these data suggest familiarity is preserved in the PD group compared to the HVs and not affected by dopaminergic medication withdrawal. The data also show a PD-dependent decline in recollection and RM, (although due to the preservation of familiarity, the RM decline is attributable to the significantly impaired recollection performance). Importantly, and consistently with study 1 of this thesis, where the PD subgroups are combined into one single cohort, results suggest that medication has no impact on the RM or recollection impairment.

4.3.6.3. Analysis of PD subgroups (PPX, RPR) compared with HVs

The PD patients, combined from study 1 and study 2 (phase 1 only) were allocated to 1 of 2 subgroups based on their D2 dopamine agonist (ropinirole [RPR] or Pramipexole [PPX], see Table 19. The raw hit and false alarm means and standard deviations for recognition memory, *know* and *remember* responses for the PD subgroups and the HVs by ON-medication/Green and OFF-medication/Blue conditions are presented in Table 22.

Table 22.

The means and standard deviations for raw hits, false alarms and mean scores for recognition memory, know and remember for the Healthy Volunteers and ropinirole and pramipexole PD subgroups across both ON-medication/Green and OFF-medication/Blue conditions.

	PD subgroups combined (n = 38)				Healthy Volunteers (n = 23)	
	Pramipexole subgroup (n = 19)		Ropinirole subgroup (n= 19)			
	Mean (SD)		Mean (SD)		Mean (SD)	
	ON-medication	OFF-medication	ON-medication	OFF-medication	ON/Green	OFF/BLUE
Recognition memory						
Hits	31.37 (7.03)	31.74 (8.61)	32.79 (8.92)	32.16 (8.32)	38.00 (5.85)	37.13 (6.16)
False Alarms	5.32 (3.68)	4.58 (3.73)	5.58 (3.91)	4.79 (3.05)	3.70 (2.79)	4.26 (3.41)
<i>d'</i>	1.61 (.33)	1.79 (.45)	1.73 (.46)	1.76 (.51)	2.20 (.57)	2.09 (.56)
Know						
Hits	12.78 (7.52)	10.16 (5.94)	11.89 (5.08)	11.21 (6.11)	9.09 (3.40)	8.04 (3.18)
False Alarms	2.94 (2.46)	2.58 (2.63)	3.84 (2.52)	2.79 (2.57)	2.52 (2.21)	2.17 (1.75)
<i>d'</i>	1.33 (.41)	1.34 (.53)	1.31 (.42)	1.40 (.56)	1.53 (.61)	1.49 (.63)
Remember						
Hits	18.53 (1.71)	22.05 (8.80)	21.74 (8.56)	21.05 (2.16)	28.04 (6.32)	29.26 (6.05)
False Alarms	2.37 (.72)	2.00 (2.03)	1.74 (2.10)	1.89 (1.73)	1.00 (1.04)	2.08 (2.94)
<i>pr</i>	.32 (.12)	.39 (.15)	.39 (.16)	.38 (.18)	.53 (.14)	.55 (.13)

Notes and abbreviations. *d'*, signal detection measure of discrimination accuracy; *pr*, threshold measure. PD, Parkinson's Disease; SD, Standard Deviation.

The mean RM (d'), familiarity (d') and recollection (pr) estimates that are presented in Figure 16 were analysed separately using a series of 3 X 2 ANOVAs. The between subjects factor was Group (HVs vs. RPR vs. PPX) and the within subjects factor was Condition (ON-medication/Green vs. OFF-medication/Blue). Significant main effects and interactions were analysed further using planned, multiple pairwise comparisons with Bonferroni corrections to control for type 1 error.

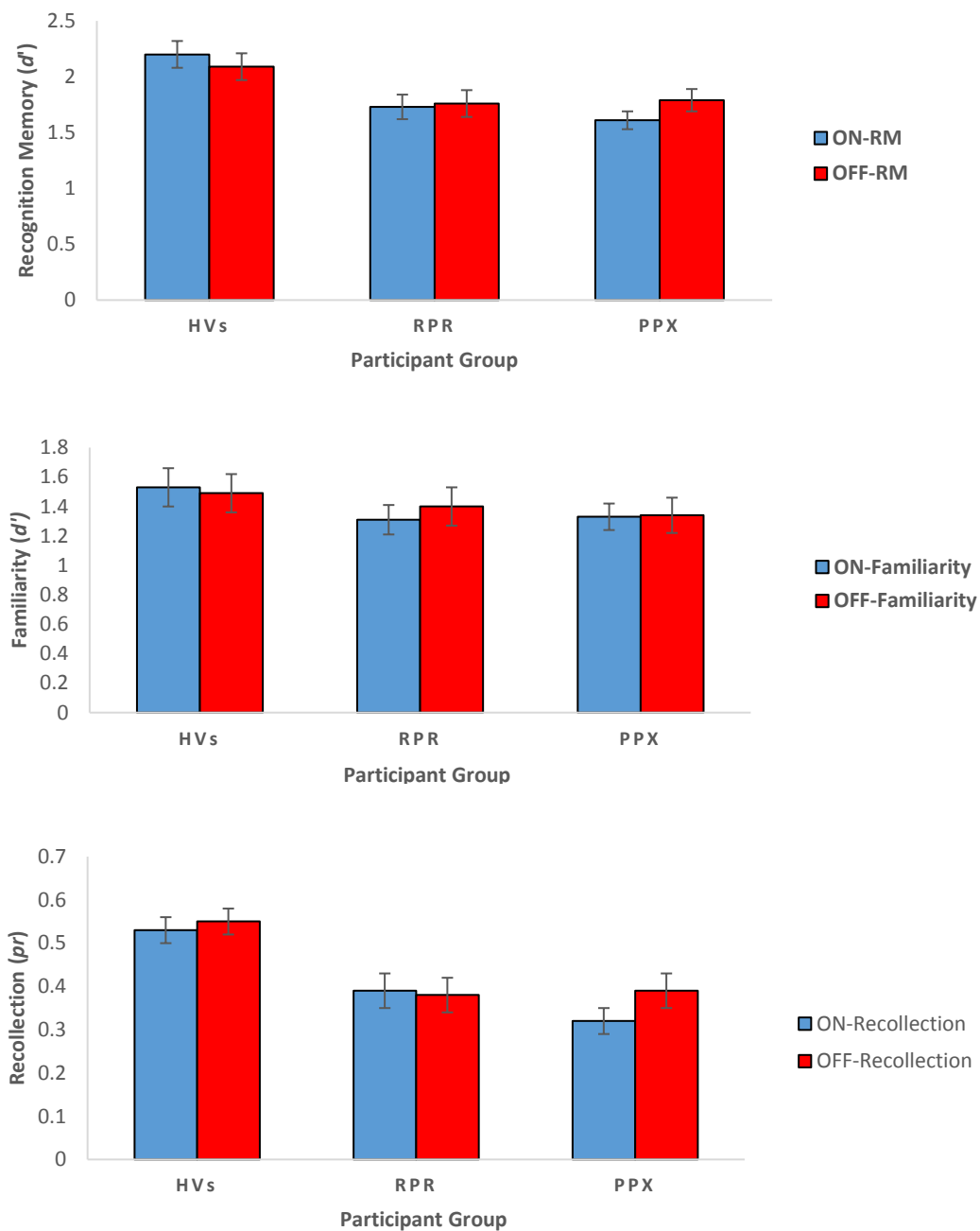


Figure 16. Estimates of recognition memory (top), familiarity (middle), recollection (bottom) and for both ON-medication/Green and OFF-medication Blue conditions by participant group with PD patients split by agonist. *Notes and abbreviations.* Error bars represent the standard error of the mean. HVs, Healthy Volunteers; RPR, ropinirole PD subgroup; PPX, pramipexole PD subgroup.

Analysis of RM (d') estimates revealed a significant main effect of Group ($F(2,58) = 6.87, p = .002$). However, there was no significant effect of Condition ($F(2,58) = 1.92, p = .59$) and the Interaction was not significant ($F(2,58) = 1.92, p = .16$). Further exploration of the significant main

effect of Group revealed that in the ON-medication condition, RM in the RPR PD subgroup ($p = .003$) and the PPX subgroup ($p < .001$) were significantly impaired in contrast to the HVs, however the two PD subgroups were comparable ($p = .42$). In the OFF-medication condition, RM in RPR subgroup was significantly impaired compared to the HVs ($p = .04$), whereas in PPX PD subgroup RM impairment only approached significance ($p = .06$). There were no significant difference in RM performance between the RPR PD subgroup and the PPX PD subgroup ($p = .85$).

For familiarity (d') estimates there were no significant main effects of Group ($F(2,58) = .91, p = .41$) or Condition ($F(1,58) = .10, p = .75$) and the Interaction was also not significant ($F(2,58) = .26, p = .77$).

The final 3 x 2 ANOVA, of recollection (pr) estimates, revealed a significant main effect of Group ($F(2,58) = 11.28, p < .001$) and Condition ($F(1,58) = 4.06, p = .04$). The interaction was also significant ($F(2,58) = 3.86, p = .03$). Planned pairwise comparisons, with a Bonferroni correction to control for type 1 error, were used to explore the significant effects further. In the ON-medication/Green condition, recollection was significantly impaired in both the RPR PD subgroup ($p = .002$) and PPX PD subgroup ($p < .001$) compared to HVs. Recollection was comparable in both the PD subgroups ($p = .78$). Similarly, in the OFF-medication/Blue condition, recollection was significantly impaired in both the RPR PD subgroup ($p = .001$) and PPX PD subgroup ($p = .002$) in contrast to the HVs and no differences between the PD subgroups emerged ($p = .10$). For both the HVs and the RPR PD subgroup there were no significant differences in recollection performance across the ON-medication/Green and OFF-medication/Blue conditions ($p = .42$ and $p = .55$, respectively). However, recollection in the PPX PD subgroup, was significantly poorer in the ON-medication/Green condition compared to the OFF-medication/Blue performance.

In Summary, with the PD group divided by D2 dopamine agonist, data suggests that familiarity is preserved in medicated and unmedicated PD, regardless of dopamine agonist. Recollection was impaired in both the RPR and PPX subgroups when unmediated, in comparison to the HVs, suggesting

a PD dependent decline. Importantly, the unmedicated recollection performance of the RPR and PPX PD subgroups were comparable, suggesting that findings are not attributable to differences in an OFF-medication state baseline. There was no significant difference in the medicated and unmedicated recollection performance in the medicated RPR subgroup, however, the unmedicated recollection impairment of the PPX subgroup further declines when medicated.

4.4. Discussion

The study presented in this chapter is a single blind, randomised controlled, crossover pilot trial, designed to compare the effects ropinirole and pramipexole on recognition memory (RM), familiarity and the recollection of episodic details during recognition in 16 patients with nondementing, mild to moderately severe Parkinson's disease (PD). This study aimed to pilot a design to inform a fully powered, definitive trial. There were 5 main aims to be explored within the pilot each of these will now be discusses in turn.

4.4.1. Exploring a phenotype, drug or phenotype*drug interaction

The findings of study 1, which suggested pramipexole induced a recollection impairment in the PD cohort studied, however the methodology that was employed left three possible scenarios which might explain the findings;

- i) A phenotype effect; a PPX effect marked by memory decline for pramipexole is only a marker, and is the agonist of choice due to the patients' motor and mood presentation. In this scenario a PPX phenotype would be present with memory impairment in the ropinirole and pramipexole treatment arm. The RPR phenotype would show no, or minimal memory decline regardless of the treatment arm they were in
- ii) A drug effect; pramipexole has a high binding affinity for d3 receptors - prevalent in the hippocampus - disrupts hippocampal dependent, episodic process through over stimulation. In this scenario all PD patients, regardless of phenotype would show memory impairment in the

pramipexole treatment arm, which would be remediated when medicated in the ropinirole arm.

- iii) A phenotype*drug interaction; a synthesis of the previous two scenarios, where the PPX phenotype is marked by a memory impairment when in the ropinirole arm, but is exacerbated when medicated in the pramipexole arm.

To explore which of the 3 scenarios most accurately explains the findings of study 1, a randomised controlled, crossover design was piloted. The data was presented in the results section in a format to illustrate using ANOVAs, pairwise comparisons and t-tests, to show how these three scenarios can be fully explored in a fully powered trial. This was not a hypothesis testing trial, however, p-values were provided for information.

4.4.2. The relationship between recollection and recall

The ultimate objective of a programme of research like this would be to help inform healthcare guidelines relating to the clinical management of PD, especially where memory disorder may be particularly prevalent. This is of particular importance should memory impairment be a result of a specific PD phenotype, or if a specific type of treatment in pramipexole which is clinically efficacious in treating the tremor and depressive symptoms of PD, may also impair memory, or if a particular phenotype, which is already marked by a memory deficit, is especially vulnerable to more severe memory disorder should they be medicated with a particular agonist. A memory assessment in clinic by the treating physician would be required, however the administration of a recognition memory test, based on the remember/know paradigm, not only requires specialist knowledge, it is a time consuming assessment and, as illustrated by the Migo et al., review (2012), the remember/know paradigm, whilst may be better than other methods of obtaining recollection estimates, it is not without its criticisms. Furthermore, a recognition memory test based on the remember/know paradigm can be complex and difficult for patients to understand, so in advanced PD, where global

cognitive decline may be present, this type of assessment may not be appropriate. As recollection is a form of recall, immediate recall and delayed recall measures of the logical memory task were included in the test battery and their relationship with recollection was assessed. Immediate recall correlated with recollection, significantly with the PD patient cohort, in both the ON-medication and OFF-medication conditions of both ropinirole and pramipexole treatment arms, whereas delayed recall did not. This would suggest that an immediate recall measure may be just as sensitive as recollection measures to memory disorder in PD and a more appropriate and accessible memory measure that could be used in a clinical setting. In a definitive trial an immediate recall measure should be included in the assessment battery, however it can be argued for the continued inclusion of a recognition memory test, based on the remember/know paradigm, as, this will help maintain a bridge to the existing PD and memory literature (Edelstyn et al., 2015, 2010, 2007; Cohn et al., 2010; Weierman et al., 2010; Davidson et al., 2006; Barnes et al., 2003; Hay et al., 2002).

4.4.3. Sample size calculations

The MeMoRY-PaD trial was a pilot to obtain recollection estimates to inform a sample size calculation for a fully powered trial. For the reasons discussed in the section above, a sample size calculation was completed for recollection and immediate recall. Using recollection as the primary outcome measure 51 PD patients would be required, but for immediate recall a sample of 137 would be required to fully explore the impact of ropinirole and recollection, across 2 potential PD phenotypes using a clinically accessible measure of recall. This number of participants suggests that a definitive trial would need to be a multi-centre trial to achieve recruitment targets and based on the recruitment rates of this pilot trial, a conservative estimate would suggest 8-10 sites may be required.

4.4.4. Combining study 1 and study 2 (phase 1 only) to increase sample size and statistical power

To address the relatively small sample sizes included in study 1. PD patients and HVs from study 1 and from this study (phase 1 only), were combined. This resulted in a total PD group sample size of 37 and a HVs group of 23. When the PD subgroup was allocated into subgroups on the basis of

their D2 dopamine agonist, there was a PPX PD subgroup of 18 and an RPR PD subgroup of 19. Recognition memory, familiarity and recollection estimates were then reanalysed using these much larger participant groups. Analysis replicated study 1 findings. Familiarity was preserved in medicated and unmedicated PD, in both the whole PD cohort and when the PD patients were divided into the RPR and PPX subgroups. Recollection was impaired in both the RPR and PPX subgroups when unmediated, in comparison to the HVs, suggesting a PD dependent decline. Importantly, the unmedicated recollection performance of the RPR and PPX PD subgroups were comparable, suggesting that findings are not attributable to differences in an OFF-medication state at baseline. As predicted, there was no significant difference in the medicated and unmedicated recollection performance in the medicated RPR subgroup, however, in the PPX subgroup the unmedicated recollection impairment declines further when medicated.

Increasing the sample size by combining the participant groups from study 1 and study 2 (phase 1 only), also increased the observed power in the analysis. Group comparisons of recollection data between PD patients and HVs was powered at 89% but this increased to 99% for the combination analysis, which show statistical power to detect even a small effect. Interestingly, the power to detect a familiarity deficit in PD was only 5% in study, this increased 40% for the combination analysis. This suggests that whilst the combination analysis would be powerful enough to detect a medium sized effect of familiarity impairment, study 1 would only have the power to detect a large PD-dependent familiarity deficit (Yuan & Maxwell, 2005). The implications of the findings from the combination analysis are discussed in more detail in Chapter 6.

4.4.5. The feasibility of using a neuropsychological test battery

A limitation of study 1 is the lack of measure of frontal dependent executive function in the test battery. Executive functioning in PD patient participant cohorts has been reported as impaired (Rodriguez et al., 2014; Edelstyn et al., 2007; Barnes et al., 2003), preserved in (Davidson et al., 2006) or are not assessed or reported in others (Weiermann et al., 2012; Cohn et al., 2010; Edelstyn et al.,

2010; Hay et al., 2002). Knowing the status of executive function in the PD patient cohorts in these studies is crucial, not only to assume that the participants are representative of the wider PD population (where even in mild PD executive dysfunction is often reported, but also traditionally, recall/recollection deficits in PD were assumed to be an extension of impaired executive functions which reflect the strategic memory processes required for the organization of material at encoding and retrieval (Moscovitch, 1994; Schacter, 1987). This can be explored with correlation between recollection/ recall and prefrontal dependent, measures, and is critical for understanding the origins of recall/recollection impairment. Of course the desire is include as many assessments as possible, however, with the objective to compare performances in ON-medication and OFF-medication testing conditions and the increased Parkinsonism experienced by participants in the OFF-medication has to be accommodated. Consequently, it is absolutely vital to be selective when selecting the assessments that comprise the testing session battery. In study 1, testing sessions that lasted a maximum of 90 minutes were deemed to be completely manageable by patients. In the MeMory-PaD trial, testing sessions were kept at that 90 minute duration. The neuropsychological battery that were selected were all well validated measures which covered a number of prefrontal domains, low demand attention, high demand attention, working memory, initiation and inhibition. This battery of tests fit timely within the 90 minute testing time period. The Test of Attentional Performance test (Zimmerman & Fimm, 2002) that was used in study 1 but was perhaps not appropriate for three reasons; firstly, the test required a response from a button press which due to the motor difficulties of participants was completed by the researcher, and performance was then measured by accuracy, instead of an accuracy/time combination, and secondly there may have been a ceiling effect, and thirdly, it took too long within the testing session, and moving it from the battery would allow for the inclusion of other executive tasks. The Test of everyday attention test has a number of subset tasks, but for the reasons discussed above, choosing them all would take too long within the testing session. The elevator counting (sustained attention task) and elevator counting with distraction task (divided attention) were chosen as they are relatively quick to do and as the latter builds on the former with

increasing difficulty, there was less risk of encountering ceiling effects, particularly in the higher demand, divided attention task, as evidenced by the data. Having an effective method of obtaining attention estimates, is essential, particularly when comparing performances on different dopamine replacement therapies to ensure any differences in recollection/recall are not attributable to an indirect negative effect of attention. This justification is also applicable for the inclusion of an apathy measure and daytime sleepiness (somnolence) measures.

The Hayling task (Burgess & Shallice, 1997) was added to the battery of tests as a well validated measure of inhibition and suppression. Both parts of the Hayling task are straight forward to explain, quick to administer and patients had no difficulty understanding the task, which is similar for the working memory tasks. The digit span working memory task is included, as evidence has shown how working memory is underpinned by the same strategic processes required for the development, selection and implementation of strategies used for the organisation of material at encoding and retrieval during a recognition memory task (Gabrili and Singh, 1996).

4.4.6. Recruitment

The fifth aim of the study was monitor recruitment to inform recruitment strategies for a fully powered trial. Recruitment was a major challenge during the MeMory-PaD trial and as a result a number of barriers were discovered which will now be discussed. The first barrier to recruitment was the pre-screening of PD patients to find eligible patients to invite into the trial. Patient recruitment was delegated to the Neurology research nurse team at the University Hospital of North Staffordshire. As there was no electronic facility that could be used to search for eligible patients based on the inclusion/exclusion criteria, like there is in primary care (e.g. with the use of EMIS codes in GP practices), this meant that paper copies of patient notes had to be manually searched, which was a hugely time consuming. A second barrier, related to the previous point, was the extremely limited research nurse capacity, which meant at various points throughout the trial there was very little pre-screening work being completed, and consequently, a slow recruitment rate. As pre-screening work

can only be carried out by personnel classed as members of the clinical care team, other members of the study team were unable to assist with this task. A number of measures were taken during the course of the trial to help support recruitment in other ways. A number of presentations were given to Parkinson's UK charity branches in the surrounding areas, specifically, Crewe/Middlewich, Chesterton/Newcastle Under-Lyme and Chester, to promote the study and a stall was attended at a Clinical Trial promotion day at the University Hospital of North Staffordshire. A half page advert was placed in the local newspaper for Stoke on Trent, 'The Sentinel' which advertised the study and interested PD patients who wanted to discuss the study in more detail were invited to contact the study team. Finally, Participant Identification Centres (PICs) were set up in local GP practices in West Midlands North Primary Care Research Network.

Potentially, the inclusion/exclusion criteria for the MeMory-PaD trial were too strict. The heterogeneous nature of PD in addition to a number of clinical, demographic and other pharmacological extraneous factors which can effect memory, suggest strict inclusion criteria are essential to ensuring that the recruited sample are a homogenous group. However, ultimately, as indicated by Table 9, 220 PD patients were screened and only 81 were eligible, having such a strict inclusion and selection criteria significantly reduced the pool of potential participants.

It was essential in this pilot to gauge the reasons for non-participation of eligible PD patients that had been invited to take part in the trial. This would allow for the identification of issues concerns, which could perhaps be rectified/avoided in a fully powered definitive trial. These barriers are the central focus of the qualitative study presented in Chapter 5.

4.4.7. General limitations of the pilot trial

As mentioned in the previous section research nurse capacity was a main challenge during the trial, but the implications of this were more far reaching than recruitment issues. Throughout this thesis, the importance of mood data has been iterated on a number of occasions, the link between memory disorder and depression, and the importance of mood in the identification of phenotyping

work. Consequently, depression and anxiety were to be measured using the Hospital Anxiety and Depression Scale (HADS), during the initial screening visit, the mid-trial hospital visit and the end of study hospital visit to assess mood changes as patient switched from one agonist to another. However, an administration error by the Neurology research nurse meant that only half of the HADS was actually administered. Consequently, no mood data (depression or anxiety) from a validated measure is available from the trial. This type of administrative error and the perhaps related issue of limited neurology research nurse capacity suggest that the use of a United Kingdom Clinical Research Collaboration (UKCRC) registered Clinical Trial Unit (CTU) to manage a full, definitive trial would be more proficient. For example, the error with the HADS questionnaire would have been identified, and therefore rectified, much sooner if monitoring had taken place earlier on in the life of the trial. The Standard Operating Procedures (SOPs) for monitoring and audit at the Clinical Trial Unit at Keele University (Research Institute for Primary Care and Health Sciences), monitor every Case Report Form (CRFs) for the first patient participant from whom data is collected. A second benefit of having the CTU manage a definitive trial is the wealth of experience clinical trial coordinators and trial managers have in managing definitive, multicentre CTIMP studies.

There appears, in the data collected in the OFF-medication sessions, a disparate performance on several measures, for example, in the PPX phenotype, when OFF-medication in the ropinirole arm (.28) and OFF-medication in the pramipexole arm (.39). A similar disparity is shown, for immediate recall, in the RPR phenotype, when OFF-medication in the ropinirole arm (24.67) and OFF-medication in the pramipexole arm (28.33). If comparable levels of withdrawal are achieved in both trial arms, a more convergent performance between these two performance measures would be expected. A reviewer response to the initial RfPB grant application suggested that agonist washout should be to 4 elimination half-lives of each agonist resulting in an approximate 93.75% washout to justify an OFF-medication testing session. As ropinirole has an elimination half-life of 8 hours, the OFF-medication testing session in the ropinirole arm took place 32 hours after the last ropinirole dose, and as the elimination half-life of pramipexole is 12 hours in a sample of this age, the OFF-medication testing

session in the pramipexole arm took place 48 hours after the last pramipexole dose. Although liver and kidney function tests were completed to ensure there at least a minimum levels clearance rate of the agonists, perhaps more work is warranted on how to achieve comparable levels of withdrawal for OFF-medication sessions that account for personal, idiopathic variability in elimination rates. One possibility for the definitive trial would be to have one OFF-medication session, before the patient enters either treatment arm. The methodology for the definite trial is discussed in the section below.

4.4.8. A definitive trial structure

The aim of this chapter was to pilot a randomised controlled crossover design trial of ropinirole and pramipexole to inform the development of a fully powered, definitive trial. Based on the recruitment rates of PD patients into the pilot trial, a multicentre trial might be required. The sample size calculations suggested that, if recollection was to be used as the primary outcome measure, a sample of 51 PD patients would be required. If immediate recall was to be used 137 PD patients would be required. If a target of 137 PD patients were set, from the MeMory-PaD trial recruitment rates, two points could be argued. Firstly, that a multi-centre trial infrastructure would be required to ensure recruitment targets were reached, with approximately 8-10 sites and secondly that areas covered by University Hospital of North Midlands may have been exhausted through the research presented in this thesis, so perhaps other trusts should be the location of the research sites.

As discussed above, the complexities and difficulties that exist around ensuring PD patients are withdrawn to comparative levels across two dopamine agonist treatment arms are apparent. However, it is still essential to have an OFF-medication testing session, to quantitatively assess the effect that the condition has on memory in isolation of any dopaminergic replacement therapy. One potential solution is to have only one OFF-medication session, but perhaps eliminating each agonist to 5 or 6 half-lives, which is much greater than what was done in the MeMory-PaD trial (and in study 1). Although having one less session would be less burden for patient-participants, having one OFF-medication after a greater period of withdrawal would probably be challenging for patients and their

caregivers and would need to be clinically managed with other forms of dopaminergic treatment with much shorter half-lives, such as l-dopa or Monoamine Oxidase B Inhibitors. A potential methodology for a definitive trial based on the MeMory-PaD trial is presented in Figure 17 below.

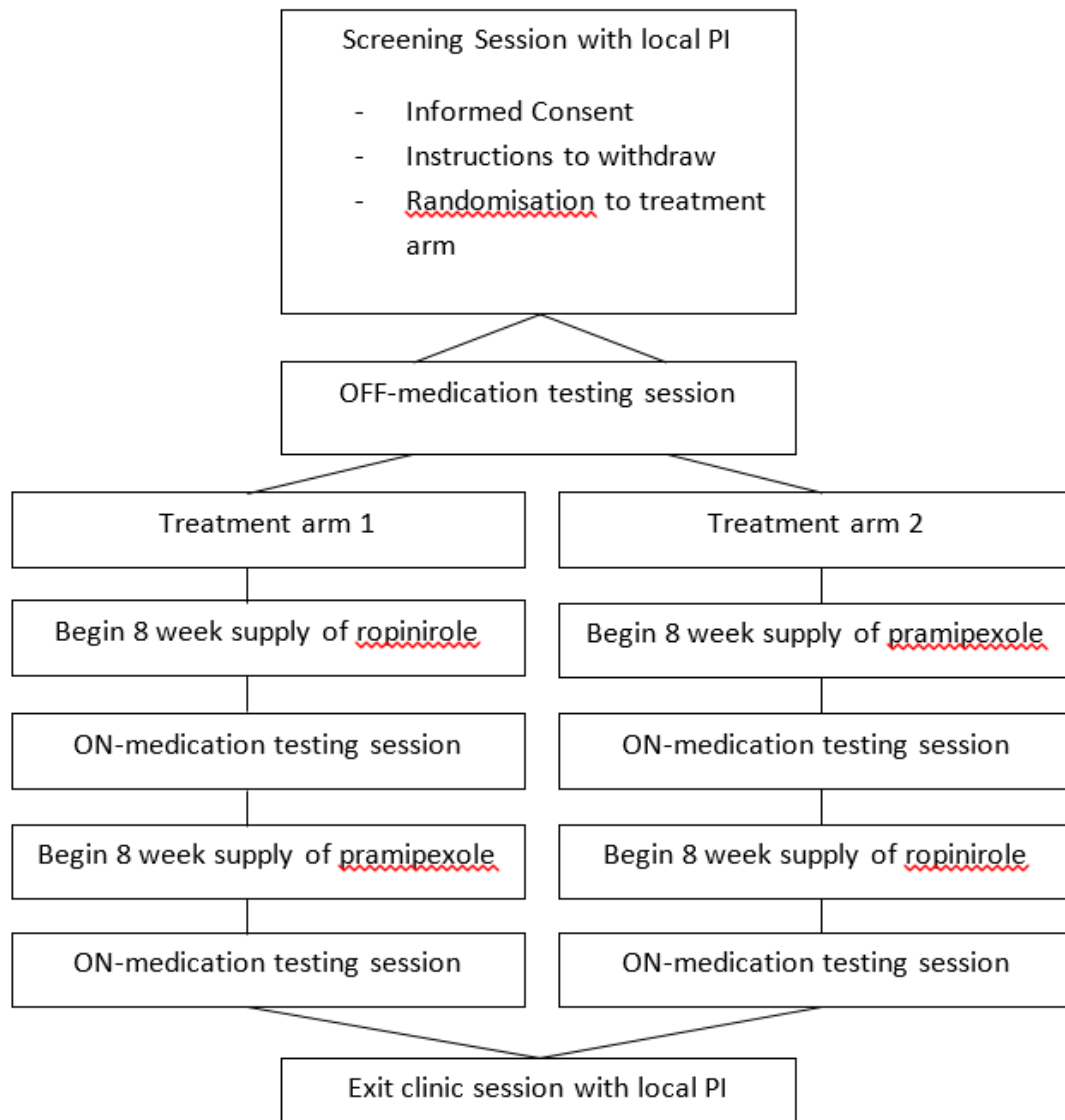


Figure 17. A flow diagram to illustrate potential methodology for a definitive trial based on the MeMory-PaD trial.

Eligible PD patients who are medicated with either pramipexole, prolonged release or ropinirole modified release as part of their daily dopaminergic regimen would be invited to an initial screening session with the local site PI, who would explain the study, assess eligibility

inclusion/exclusion criteria and take informed consent. Whilst at the screening, the patient would be randomised to 1 of 2 treatment arms, but would not start any study medication at this point. Firstly, the PD patient would have an OFF-medication testing session with the researcher and undergo tests of recognition memory, recall depression and anxiety, tests of motor functioning and executive function. Once completed, the patient would start the study medication from which ever treatment arm they were randomised to during the screening. In treatment arm 1, the patient would start an 8 week pack of ropinirole. Clinical guidelines still suggest that a 6 week stabilisation period is required when starting a new dopamine agonist. This leaves a 2 week window for a research session to be arranged whilst still on the study agonist. A matched battery of tests to the OFF-medication session would be administered to the PD patient, one hour after they had taken their first dose of medication that day. Then the PD patient would switch to the second study drug in treatment arm 1, which is pramipexole. Again, after a 6 week stabilisation period they would undergo the same battery of tests, before an exit visit with the local site PI. During this exit visit, the patient can feedback to the PI, which of study drugs they found to be the most effective in controlling their PD symptoms, giving the patient the opportunity to discuss perhaps staying on an agonist which is different to the one they may have taken as part of their daily regimen prior to entering the trial. There is the potential for this to be double blinded, so that both the researcher administering the tests and the patients are blinded to which treatment arm they are in, which would increase the validity of the study data.

5. Chapter 5. Investigating the barriers to participation in a randomised controlled crossover trial of ropinirole and pramipexole: A qualitative study with eligible patient decliners and their caregivers.

5.1. Introduction

Clinical trials are essential for assessing the efficacy or tolerability of drug therapies, interventions and diagnostic tests (Mathur, DeWitte, Robledo, Isaacs & Stamford, 2015). Randomised controlled trials (RCTs) remain the gold standard methodology in research and are critical for obtaining information about a condition, how it manifests and its clinical course. The rising importance of evidence-based practice means that clinicians increasingly use the results of RCTs to make decisions about the clinical management of their patients (Sackett & Rosenberg, 1995).

Obtaining the reliable and valid results required to inform the clinical management of patients is hugely dependent on the timely recruitment of an adequate homogenous sample of the trial's target clinical population. However, recruitment remains one of the main challenges facing clinical trials. It is frequently more difficult and proceeds at a slower rate than originally forecasted and many RCTs fail to reach the required sample sizes in the timescales initially predicted, in fact 45% of clinical trials are delayed because of the challenges in recruiting participants (Stephenson & Bhamal, 2010). A meta-analysis revealed that only 31% of RCTs successfully completed the originally forecasted recruitment in time, half of which requested an extension to recruit to a sufficient sample size (McDonald, Knight, Campbell, Entwistle & Grant, 2006). However, despite granted extensions, only a small minority still managed to recruit to target, suggesting the trial design is unattractive to participants and/or the implementation of sub optimal recruitment strategies (Picillo, Kou, Barone & Fasano, 2015).

There does appear to be discordance between patient perceptions about their likelihood of taking part in clinical trials and reality. In a US clinical research poll (2013) 72% of responders declared they would take part in a clinical trial if recommended by their clinician, however only 16%

had ever taken part in one. This discordance is present in the PD literature, in a survey of 823 PD patients for the Michael J Fox Foundation for Research in 2011, over 80% of PD patients reported they were at least “somewhat likely” to participate in a clinical trial, however only 1 in 10 patients had actually ever taken part (Meunier, Chowdury, Cappelletti & Sherer, 2014).

Of course one way to increase the numbers recruited into trials is to increase the number of those approached – simply widening the net. Attempts to develop a number of initiatives to be more inclusive in recruitment practices, such as approaching more rural dwelling patients (Anuruang, Davidson, Jackson & Hickman, 2015) and using internet based technologies, such as telemedicine (Shprecher, Noyes, Biglan, Wang, Dorsey, Kurlan et al., 2012). Whilst both of these initiatives have been shown to be successful in increasing the numbers of potential participants approached, the implementation of extra recruitment strategies within clinical trials are accompanied with increased costs, technological requirements and staffing needs.

Investigations as to why patients decide to participate in clinical trials have generally yielded consistent findings across a number of quantitative and qualitative methodologies. In a survey of 207 non dementing PD patients entering RCTs across a 5 year period, over 63% of patients declared that the desire to help advance scientific knowledge about PD was their primary motivation to participate in clinical trials, 56% noted the access to potentially better treatment options and 52% suggested it was on the recommendation of their consulting neurologist (Valades, Coelho, Mestre, Guedes, Finisterra & Noronda, 2011). Qualitative approaches with study teams (Newington & Metcalfe, 2014) and patients (Lawton, Fox, Fox & Kinmonth, 2003) suggest participation in clinical trials relies on 3 major domains. 1) Altruism - the desire to help other patients as well as their regular clinician and hospitals where they are treated. 2) Personal health benefit – patients are motivated to join clinical trials as they believe they can gain access to ‘better’ treatments to improve symptoms. Further, the regular monitoring and health care appointments with their clinicians are attractive to

patients. 3) Patient trust/familiarity – particularly in the research team and the institution where the research is being undertaken.

Recruitment challenges are particularly relevant in older populations (Bartlam et al., 2012) and the heterogeneous nature of PD means that achieving a sufficient homogenous patient sample requires the implementation of very effective recruitment strategies. PD patients are often elderly and disabled, therefore participation in clinical trials will require the assistance of a caregiver, not only with (hospital visits, organising medication etc) but also in the decision to participate itself.

For drug trials in particular, PD patients have positive perceptions of placebo controlled trials, although they are strongly in favour of receiving the active agent (Valadas, et al., 2011; Goetz, Janko, Blasucci & Jaglin, 2003). Furthermore evidence suggests a preference for trial designs which include two active agents (or an active comparator) over placebo controlled designs and that this may facilitate recruitment due to patients being less likely to experience lessebo effects (the negative expectations associated to the administration of a placebo) (Mestre, Espay, Marras, Eckman, Pollak & Lang, 2014).

Mathur, DeWitte, Robledo, Isaacs and Stamford (2015) surveyed 197 PD patients and 41 caregivers to PD patients and asked them to pick their 5 main reasons for non-engagement with clinical trials. Mathur et al., (2015) report that whilst results were varied, the most significant barriers were ‘the potentially adverse consequences/side effects of taking part in clinical trials’ (56%); ‘the disruption to current medication regimes’ (53%); ‘I may be given the placebo and not the real drug’ (38%); ‘The upheaval to my life that the trial would cause’ (37%) and ‘Being kept fully informed of both the progress and results of the trial when appropriate’ (34%).

The MeMemory-PaD trial presented in the previous chapter (see Chapter 4 for a full study description), had a particularly low conversion rate of approached potential participants to fully consented trial participants (27%), which is typically low for clinical trials involving elderly participants (Bartlam, Crome, lally, Beswick, Cherubini, Clarfield, Edbrooke et al (2012). The purpose

of the study presented here, was to qualitatively explore the perceived barriers to participation from eligible PD patients who were invited to take part, but declined ('decliners'). Health care decisions for individuals with long term conditions such as PD are often involve input from a caregiver and/or other family members too. Consequently, caregivers of patient decliners were also approached. The primary aim of conducting this study was to identify the most serious concerns expressed by patients and their caregivers, to see if in future trials these concerns could be mitigated to make trials as accessible as possible and to improve the conversion rate of approached eligible participants and those that become fully consented trial participants.

5.2. Method

5.2.1. Design

A qualitative approach was used to explore the barriers to participation in the MeMory-PaD clinical trial (a randomised controlled, crossover design clinical trial, for full description of this study, see chapter 3). Interviews are an appropriate method for collecting rich subjective data, by permitting patients and caregivers to talk openly and discuss in detail, if they wished, about the concerns they had about taking part in the MeMory-PaD trial. A semi-structured interview schedule was used to guide the interviews. Questions included 'What were the concerns you had about taking part in the clinical trial?', 'Have you ever switched medication previously?', 'Were you familiar with the research team prior to hearing about this study?' and 'Did you understand what the study was about?'. Not all of the questions on the schedule were asked, particularly if the participant had already covered that topic. As a result of this, the order of the discussion points on the interview schedule was not always the same. Open ended questions provided an interview framework flexible for both interviewer and participants, and the freedom to explore specific details relating to the concerns about participation. Prompts were used to elicit more details from participants when necessary. The study received ethics approval from the Greater Manchester Central, National

Research Ethics Service and approval from the University Hospital of North Midlands, Research and Development department.

5.2.2. Participants

A qualitative approach was used to explore the barriers to participation in the MeMory-PaD clinical trial (a randomised controlled, crossover design clinical trial, for full description of this study, see chapter 3). Interviews are an appropriate method for collecting rich subjective data, by permitting patients and caregivers to talk openly and discuss in detail, if they wished, about the concerns they had about taking part in the MeMory-PaD trial. A semi-structured interview schedule was used to guide the interviews. Questions included 'What were the concerns you had about taking part in the clinical trial?', 'Have you ever switched medication previously?', 'Were you familiar with the research team prior to hearing about this study?' and 'Did you understand what the study was about?'. Not all of the questions on the schedule were asked, particularly if the participant had already covered that topic. As a result of this, the order of the discussion points on the interview schedule was not always the same. Open ended questions provided an interview framework flexible for both interviewer and participants, and the freedom to explore specific details relating to the concerns about participation. Prompts were used to elicit more details from participants when necessary. The study received ethics approval from the Greater Manchester Central, National Research Ethics Service and approval from the University Hospital of North Midlands, Research and Development department.

5.2.3. Procedure

All interviews were conducted by the researcher, at the patient/caregiver's home for their convenience. Interviews were recorded using a digital recording device; all recordings were transcribed verbatim after the interview by the researcher. This was highlighted to participants in the participant information sheet (Appendix X) and prior to the start of each interview to ensure that they were fully aware of the ethical issues relating to the interview.

Participants signed two consent forms prior to the start of the interview, a standard form to indicate they understood the purpose of the study and that they agreed to take part (Appendix Y) and a second form regarding the use of anonymised direct quotes (Appendix Z). Participants were also reminded that they should only discuss topics they were comfortable with and that breaks could be taken if needed. Interviews lasted between 20 – 30 minutes. Once each interview was completed participants were thanked and given the opportunity to ask any questions they may have.

5.2.4. Data analysis

Interview recordings were transcribed by the author. During the transcription process initial thoughts and observation were noted. Accuracy was checked by listening to each recording whilst reading through the respective transcript and any necessary amendments were made. The interviews were transcribed into Microsoft Word.

Interview data were analysed using thematic analysis, an appropriate procedure for distilling qualitative data to identify common themes and is used across a large range of research topics, from large and small datasets (Braun and Clarke, 2006). The 6 stages recommended by Braun and Clarke (2006) for thematic analysis were followed; familiarisation with the data; coding the data; searching for themes; reviewing themes; naming themes and writing up the findings. Analysis was also guided by further recommendations by Attride-Stirling (2001) and Braun and Clarke (2006). Firstly, after initial identification of basic themes, refinement of those themes was constant as a result of new, relevant pieces of transcripts that were read and better understood. In some cases themes were made broader to accommodate relevant data extracts or were merged together if they overlapped and/or contained the same piece of transcript. Secondly, Braun and Clarke (2006) recommend that qualitative data analysis should not follow a linear process and that re-reading transcripts after the development of new themes should be common practice and that steps used throughout the analysis should be repeated.

A software package was not used to analyse the data as other qualitative researchers recommend that more manual methods, especially for studies with a small sample size. Walsh (2002) and Bringer, Johnston and Brackenridge (2006) indicate that qualitative data analysis software packages, such as NVivo 7, are perhaps more appropriate for organising the data and analysis processes like coding but not for actual analysis. One limitation of using software packages to analyse the data is that researchers can frequently bypass essential components of the data which influence identified themes as they become preoccupied with the number of data pieces or the size of the data pieces in a particular theme (John & Johnson, 2000). As a result Microsoft Word was used. Initial topic coding was achieved by reading through the transcripts and detailing basic themes within the text using the Microsoft Word comment function. New themes emerged from the data throughout this process, so to ensure accuracy the procedure was repeated to ensure that text from transcripts that had been read prior to newly developed themes could be subsumed under the appropriate theme. (An example of 1 transcript, with analysis is provided in Appendix AA).

5.3. Results

Four main themes emerged from the interviews with patients and caregivers which represented significant barriers to participation in the clinical trial. The 4 main themes together with each of the sub themes, along with illustrating quotes are presented in Table 23. All participants contributed to each of the 4 main themes, but not necessarily to all sub themes.

Table 23.

The main themes and subthemes capturing the barriers to participation in the MeMemory-Pad randomised controlled, crossover clinical trial.

Switching Medication	<p>A risking to stability – ‘It takes a long time to get stable, I didn’t want to mess with that’ (px3);</p> <p>Previous switching experience – ‘I felt terrible for 6 months’ (px1), It was quite hard, I was quite poorly’ (px3); I didn’t want to start having side effects again. (px4)</p> <p>Irreparable deterioration – ‘these [tablets] allow us to live our lives. You don’t to start messing with that in case you can’t get it back (px4);</p>
Trial Accessibility	<p>Patient information sheet – ‘It was a bit “sciencey”’ (cg1); ‘it was long [...] it took some effort to read’ (cg2); ‘it is too complicated’ (px5)</p> <p>Inconvenience – ‘the hospital trips, we weren’t keen on the driving (px1); with all the visits, fitting it all in would have been difficult for us (cg2)</p>
Fear of unknown	<p>Research process – ‘I thought that it was quite a complex study.’ (px2) ‘I thought it meant testing brand new drugs.’ (px4)</p> <p>Research team – ‘I think there is a trust thing isn’t there.’ (cg3) ‘I suppose others would be more comfortable.’ (px3)</p>
Caregiver workload	<p>‘her getting worse was a problem for me, because it would be a problem for me.’ (cg3)</p> <p>‘If I got worse then he would have to help get about you see. I don’t like to ask him to do more for me.’ (px3)</p> <p>‘I would have had to help her about the house a lot more.’ (cg3)</p>

Notes and abbreviations. cg, caregiver participant; px, Parkinson’s disease patient participant.

Switching Medication

All participants discussed a serious concern over switching their PD medication as the primary barrier to participation in the trial. It was a major concern for both the patient decliners and their caregivers. Three sub themes were identified and are discussed below.

A risk to stability. When the prospect of switching medication was raised in the interviews, it was clear that switching medication posed a threat to any current stability, or consistency they received from their treatment

‘Just the medication really. I really didn’t want to change medication, as Im good at the moment, I haven’t been this good for a while. I thought I don’t want to get worse if I change medication [...] It takes a long time to get stable on your tablets. I didn’t want to mess with that. [...] it’s the best I’ve been for a while.’ (px3)

To patients, stability, and the ‘known’ effect of ‘their’ medication is clearly of vital importance. To potentially lose that is not something to be taken lightly.

‘Oh yes, it’s the most stable I’ve been for a while. That’s why I didn’t want to risk that [...] you know we rely a lot on our tablets doing what we expect, you know, these allow us to live our lives.’ (px4)

The impact of a different treatment, or losing that ‘known’ stability has consequences for patient’s daily lives and activities. Something that is just as important for spousal caregivers as well. Reflections suggest that the known stability is more valuable than the risk of not being treated as well, or than the potential for improvement.

‘When it’s not so stable, it’s terrible. You don’t want to leave the house in case you freeze somewhere or fall over or something like that. You lose your confidence you know?’ (px4)

‘You know, it’s not easy to mess about with medication; it’s like her life blood, so why change what is working? [...] it seemed too risky, you know, too much of a risk to play with that.’ (cg3)

One caregiver highlighted the importance of stability and how widespread the effects of instability can be, not just for the patient, but the spouse and the rest of the family.

‘I wouldn’t like it if he was on an even keel on his current medication, bearing in mind the negative responses to drugs in the past. The fact that you might bring in another drug that would negatively influence where he’s at the moment, and because, it not only affects, his symptoms of Parkinson’s but it also affects his emotional wellbeing, his attitude to life, his responses in the family and so forth. You know, how he’s sleeping, how low he is in spirit and all that sort of thing. And if he’s in a situation where he’s running well, I wouldn’t want that changed.’ (cg3)

Previous negative switching experience. Patients discussed negative experiences from switching from their current medication, or from the initiation of new PD drugs in the past. When asked about switching previously, patients generally described it as a negative experience:

‘Oh yes, that was why I didn’t take part really as I had only just got my medication sorted really. I was all over the place for 6 months, I felt terrible really, especially in the morning. I couldn’t walk at all really. I really struggled actually, I would get stuck all the time, doorways, or getting in and out of the car. It was quite a worry. I was like that for a while to be honest.’ (px1).

The illness or severity of PD symptoms, or additional side-effects during, previous drug switching was something participants wanted to avoid.

‘It was quiet hard, I was quite poorly with it, and the tablets didn’t seem to work at all at first. That’s when my Parkinson’s was at its worse I think. I didn’t want to go through that again.’ (px3)]

‘Horrible. I mean, no other word for it. And it takes so long to come off it- you’re sort of 6 weeks down 6 weeks up. Erm, yeah, not nice. It’s the side effects I Think. Just feeling unstable and everything else.’ (px5)

Participants made it clear that it’s not necessarily switching medication per se, but even the initiation of new types of medication into an existing regimen can bring with it additional side effects and symptoms for a time, which have implications for patient’s mobility and ability to complete daily activities/tasks.

‘No but I have started news ones, you know extra to what I’m on. It can be really hard going. I didn’t want to start having side-effects all over again. Or to feel worse, because that would stop me from doing the things I want to do you know? I like to get out and have a walk, do the garden, you know, bits around the house.’ (px4)

Irreparable deterioration. Some participants not only discussed the worsening of symptoms whilst in the trial as a barrier to participation, but perhaps more critically and more worrisome, a genuine concern that any worsening of symptoms as a result of either being in the trial, or the trial medication may be something they might not recover from.

‘these [tablets] allow us to live our lives. You don’t to start messing with that in case you can’t get it back.’ (px4)

This was not just a concern for the patients; the impact of a progression in disease severity was a concern for the caregivers too.

‘if she got worse and it made the Parkinson’s worse, and then it couldn’t be fixed again.’
(cg3).

Trial Accessibility

A second major theme in the data related to how accessible the trial was for potential participants and their caregiver. Two sub themes were identified.

Patient Information Sheet. Participants indicated difficulties with the patient information sheet that was sent as part of the initial study invitation pack that was sent to eligible patients to invite them in to the trial. Every participant particularly commented on the length of it.

‘It was very long I thought, and the language was hard to understand (px3)

‘I bet people lose interest halfway through.’ (px4)

Not only the length of the patient information sheet was an issue, participants also discussed how difficult they found it to understand the language that was used

‘Well it was just very long. I didn’t read it all at once and I know that (WIFE) didn’t either.

[...], some of the jargon was tricky.’ (cg3)

‘There was a lot on information to take in. I thought the some of the language was a bit

‘sciencey’ for us simple folk though. So we didn’t understand all of it.’ (cg1)

One patient whilst finding the information understandable himself, suggested other people would find it much more difficult

‘I understood it. I’m sure others might struggle with some of the science language.’ (px2)

Participants realised that certain information needs to be included but had very clear ideas about how it would be more accessible.

‘make it shorter, and more direct, and in the jargon that the average person probably could understand. Sometimes, these sort of things are, become complicated, trying to fill up all the

boxes, and you know, tick all the boxes and what have you do. I think the longer a thing is, the quicker people will turn off, not fully, involved.’ (cg4)

Inconvenience. Participation in the trial involved a total of 8 appointments over a 16 week period. Some of which had fixed time points. Some participants felt that this was too difficult to fit in around other time commitments.

‘We go away a lot. And it would have been difficult to go away and have all the sessions and visits I think. [...] It would have been quite inconvenient for us.’ (px2)

‘we discussed the hospital trips, we weren’t keen on the driving.’ (px1)

‘It was just there was a lot to do and we had holidays booked. So with all the visits, fitting it all in would have been difficult for us [...] I thought, what if we run out of the drugs whilst we were away? Things like that were important.’ (cg2)

Fear of the unknown

For many participants they had never previously taken part in any research prior to the interview. Taking part of this of course means that any form of research is going to be complete unknown prospect. Clinical trials in particular, can be complex and have significantly risk, and burden, two subthemes were identified in the data in relation to being unfamiliar with taking part in research, the research process itself and an unfamiliarity with the research team personnel. These subthemes are discussed below

Research Process. Unfamiliarity with the research process undoubtedly causes anxiety in potential participants and provided a barrier to participation for the decliners.

‘I thought that it was quite a complex study.’ (px2)

In particular, clinical trials can be complex, and daunting for participants who have never taken part in any research previously, one caregiver suggested that taking part in a less complex study first, before

‘We would but I think that we would want a study we felt more comfortable with first [...] maybe without switching medication [...] So we can understand how it all works a bit better first. You know, before doing something more complicated [...] we might be better taking in part in easier studies first, you know so we can know the process better.’ (cg4).

A number of participants discussed how their understanding of what a clinical trial is had been a major barrier and cause for concern.

‘Well I must admit, I thought it meant testing brand new drugs.’ (px4)

‘I thought it mean trying new drugs, you know that have been invented. When I first saw this I thought that is what it was. Which made me panic slightly because I would be worried about (WIFE) taking a drug that hadn’t been tested before, you know? Switching tablets is bad enough, but to completely new ones, that would be a little too much.’ (cg3)

Furthermore, there was lack of familiarity with the care team/procedures that were in place (and detailed in the information sheet) in case of any bad reactions to any medications or if a patient became unwell whilst in the trial. Making this information more explicit in the patient information packs may mediate some of the concerns participants have already expressed.

‘Oh right, I didn’t know, that’s a good idea. If I was going to change my medication I would want that. Yeah I would want that.’ (px3)

‘I think I read it in the information. Maybe it should be more apparent and obvious though, you know to reassure people.’ (px4)

Research Team. A lack of familiarity with the research process extends much further. Participants also discussed how important a prior relationship with the research team might be in recruiting participants into the trial.

‘Oh yes, I think that would be a lot better. I think there is a trust thing isn’t there. Like if we had been a part of things before with the same people that would be a lot better,’ (cg3)

‘I would think if people, were more comfortable they would be willing to give more. Maybe do studies where they are more vulnerable maybe, or more at risk.’ (px4)

‘I suppose others would be more comfortable if they had taken part in research for before, or if Dr Ellis (CI) is your consultant, others may be more comfortable.’ (px2)

‘Yes I think so [...] People are more likely to put themselves out for people they know.’ (px3)

Caregiver Workload

A fourth major theme in the participant data was a concern that taking part would increase the amount of work that the caregivers do on behalf of the patient. Caregivers often drive for the patients to get around, and with the additional trips to the hospital involved in the trial this would be a significant extra burden:

‘driving to the hospital I think is one.’ (cg3)

Also a number of caregivers were responsible for the arranging the medication that the patient takes throughout the day, there was a patient concern on the caregivers behalf, that having different medication to arrange would be extra work:

‘she (WIFE) puts my medication out, so she would be in charge of that for sure.’ (px2)

‘taking me to the hospital, but maybe. It depends. If I got worse then he would have to help get about you see. I don’t like to ask him to do more for me. (px3)

Perhaps the greatest concern in relation to caregiver workload was the extra burden that would fall on the caregiver, should the patient get worse or become ill during the trial.

‘her getting worse was a problem for me, because it would be a problem for me.’ (cg3)

‘driving to the hospital I think is one thing I would do, [...] I think that’s it. I mean if we had have taken part and she got worse, you know physically, then I would have had to help her about the house a lot more, you know to get about and stuff, if she had got worse.’ (cg3)

For one patient, the risk of getting worse and being even more dependent on the caregiver was a significant barrier to participation

‘Taking me to the hospital, but maybe. It depends. If I got worse then he would have to help get about you see. I don’t like to ask him to do more for me.’ (px3)

5.4. Discussion

The purpose of this study was to explore the barriers to participation in the MeMory-PaD trial by conducting semi-structured interviews with patients who declined to participate and their caregivers. Four major themes were identified: ‘Switching medication’, ‘Trial accessibility’, ‘Fear of the unknown’ and ‘Caregiver workload’. One strength of this study is the frequency at which these themes were present across participants, despite the heterogeneous presentation of the patient participants, and regardless of gender.

The first theme to be identified was ‘*Switching Medication*’. This theme overarched the most serious concerns that patients and their caregivers had about participating in the trial. It was apparent from participant accounts that achieving daily functional stability with their PD medication, which allowed them to complete their daily activities is something that not only takes time to reach, it is also something that is not worth risking by switching their regimen, based on the severity of symptoms and difficulties experienced during times when things were less stable. Furthermore,

patients who had switched medication previously generally regarded this as a negative experience, with a reduced ability to complete their daily activities, an increase in the severity of their PD symptoms, distressing side effects and a general feeling of poor health. These concerns are consistent with findings within the literature which have explored barriers to RCT in PD patients (Mathur et al., 2015, Picillo et al., 2015). Mestre, et al., (2014) suggest that a comparable active agent may facilitate recruitment in clinical trials, however, this was inconsistent with the participant accounts in this study. Furthermore, accounts of why patients take part suggest that potential health benefits from alternative medications as a primary motivating factor (Newington & Metcalfe, 2014; Lawton et al., 2003). However, from the accounts of the PD patients in this study, the risk of negative outcomes from participation in a clinical trial may outweigh the potential for improvement, and consistent, or 'known' effects from their PD medication may be more acceptable. Implications of the severity of the concerns subsumed within this theme suggest a critical need for research teams to clearly communicate with potential patient participants about the likelihood of adverse events of trial medication and to ensure a visible presence of care procedures in study documentation should patient experience a worsening of symptoms or side effects.

The second identified theme '*Trial Accessibility*', related to difficulties patients and caregivers had understanding the patient information sheet, and therefore their role in the trial itself. Participants had discussed the complexities with not only the length of the information, but the complexity of the language itself. Much of the content for information sheets for clinical trials is dictated by National Research Ethics Committee requirements, and with a randomised controlled, crossover trial, a lot of information is required to inform readers. The patient Information sheet for the MeMory-PaD trial was 9 pages long, and a Patient Participant Involvement (PPI) group had assessed the accessibility of the terminology as acceptable. However, from the participants in this study, a primary objective for researcher teams, should be to develop alternative and innovative methods of sharing study information to patients so that it can be consumed in an accessible way, the use of internet technologies (Shprecher et al, 2012) and more recently, Apple's 'Researchkit'

have already shown promising results. The clarity of information is particularly important in PD where cognitive decline may be present (Karlawish, Cary, Moelter, Siderowf, Sullo, Xie et al, 2013). Furthermore patients and caregivers acknowledge that taking part in the trial involved a number of inconveniences, primarily the number of appointments within the 16 week period. This compliments recommendations from Picillo et al., (2015) when designing more attractive clinical trials in that study protocols should endeavour to minimise the number of hospital visits/testing sessions required and the length of time that patients are 'active' in a trial. However, achieving this without compromising the scientific quality of the trial design remains a significant challenge for research teams.

The third theme from participant data, '*Fear of the unknown*' encompasses significant barriers to participation, firstly with the research team and secondly, unfamiliarity with research processes for those who have previously never taken part in research. The emergence of this barrier is consistent with previous evidence that PD patient would be more likely participate in clinical trials if a member of their clinical care team recommended it (Valadas et al., 2011). A particular issue in PD as a Harris Poll survey conducted on behalf of the Michael J Fox Foundation showed, that awareness of clinical trials to recommend patients to is especially low in consulting neurologists, in fact the majority had never recommended a trial to their patients - only 47% of consultants had referred patients directly into a trial, and 37% were unaware of any trials operating in their geographical area. The importance of prior relationship with the research team was expressed in the participant accounts in this study (Mainous, Smith, Geesey & Tilley, 2008). The lack of familiarity with the research team implies that the use of passive recruitment strategies are insufficient and more active methods may prove more successful in helping to increase the presence of the research team and build a familiarity and trust. It is therefore recommended that research teams work to build a visible presence in their local community, and should promote and publicise their research activities within the community, not just typical avenues of academic dissemination.

The final, fourth theme '*Caregiver Workload*' described how there was a very real concern by caregivers themselves and by patients on behalf of their caregivers that participation would increase their workload and burden. For the majority of the dyads in the participant group, caregivers had the responsibility of organising the patient's medication, attributed to difficulties accessing the tablets from the packs due to patient motor symptoms and the patient's forgetfulness. Concerns were expressed that complicating this procedure by switching medications out for more unfamiliar tablets increased the workload for caregivers. Similarly, participation meant more driving for caregivers to make the number of hospital trips, which is unattractive prospect for caregivers. Perhaps the most concerning aspect for caregivers was the extra burden on them should their spouse experience an increase of disability during the trial. This was something expressed not only by caregivers but from the patients too, the guilt experienced by patients for asking for extra assistance should they experience a worsening of symptom presents a significant barrier to participation in clinical trials. Acknowledgement of the role of the caregiver, not only in contributing to the decision to take part, but also in assisting the patient with trial commitments, will be essential for research teams when designing trials, and where appropriate, caregiver support may help alleviate this participation barrier.

The fact that this was small study and that the barriers to participation that were identified were specific to those who declined to take part specifically in the MeMory-Pad Trial, not research or clinical trials in general, may limit the generalisability of the results. Nonetheless, this study has generated valuable findings about patient and caregiver concerns relating to participation in research generally, and specifically in randomised controlled, crossover, clinical trials. Some of the themes that were identified in this study have complimented findings in other investigations and have specified major concerns that potential participants have about clinical trial participation. Attempts can be made by research teams to mitigate these barriers to reduce patient and caregiver concerns and consequently increase recruitment rates.

The success of a clinical trial is heavily dependent on research teams overcoming recruitment challenges. The timely recruitment of an adequate sample size is essential to add reliability and validity to trial findings, reduces the need for costly extensions, and safeguards trials from higher than expected attrition rates. The scientific community have a vested interest in learning from decliners so that pertinent patient concerns can be mitigated in the design of future trials. Whilst initiatives to increase the inclusivity of recruitment strategies have shown to have positive outcomes by achieving recruitment targets by increasing the number of eligible patients initially approached, the alleviation of patient and caregiver concerns should not be neglected to increase the conversion rate of eligible potential patients approached into fully consenting participants in clinical trials.

6. Chapter 6: Future directions for research into memory disorder in PD using Clinical trial methodologies

The overall purpose of this thesis was to explore and compare the effects of dopamine agonists, ropinirole and pramipexole on recognition memory, specifically familiarity and recollection, in idiopathic PD. Firstly, this was done by comparing two clinically matched groups of PD patients, one medicated with ropinirole and another medicated with pramipexole (study 1). The findings of study 1 (chapter 3) suggested that pramipexole induced a recollection impairment in those PD patients compared to when they were tested after a period of medication withdrawal (OFF-medication). Furthermore, the PD subgroup medicated with pramipexole, were significantly poorer in comparison to the subgroup medicated with ropinirole. However, as illustrated in the introduction section of chapter 4, there were several limitations and unanswered questions as a result of the methodology that was used, which required further investigation.

So to explore the study 1 and the combination analysis findings further, the second aim of the research presented in this thesis was to pilot a randomised controlled, crossover trial design, to compare both ropinirole and pramipexole in the same group of PD patients. The pilot trial had a number of purposes; to illustrate how the data can be analysed to explore the 3 potential scenarios which would contribute to the unanswered questions which remained as a result of the limitations of study 1. Secondly, to assess if a more clinically accessible measure could be used as opposed to recollection. Thirdly, to calculate sample sizes required for a fully powered definitive trial and fourthly, to assess the feasibility of a neuropsychological tests battery used in each of the testing sessions. The exploration of these aims led to a design of a fully powered definitive trial which was outlined in the discussion section of chapter 4. The fifth aim was to monitor recruitment throughout the life of the trial. The exploration of the barriers to recruitment in the trial was the focus of the study 3, described in chapter 5.

One of the main challenges to any clinical trial of investigational medicinal product is recruiting an adequate sample size, to add the validity to findings which is required to influence evidence based practice (Mathur, DeWitte, Robledo, Isaacs & Stamford, 2015). PD patients who were eligible but declined to take part in the MeMory-PaD trial, and their caregivers, were asked to take part in separate interviews to discuss what they felt were the main barriers to participating in the trial. The purpose of this study is to understanding why eligible, potential participants decline to take part in the pilot trial to inform the development of a fully powered definitive trial.

The findings of study 1, and the combination of study 1 data with study 2 (phase 1 only) support previous evidence from studies adopting a dual process model of recognition memory which report a recollection impairment but preserved familiarity in PD (Edelstyn et al., 2015; Rodriguez et al., 2014; Edelstyn et al., 2010; Algarabel et al., 2010; Edelstyn et al., 2007; Barnes et al., 2003; Hay, Moscovitch & Levine, 2002), but contradict studies which have reported a preserved recollection but impaired familiarity (Cohn et al., 2010; Weierman et al., 2010; Davidson et al., 2006). The meta-analysis of these previous studies (presented in section 2.3.) suggested a recollection impairment with a strong effect size, a familiarity decline, with a medium effect size. There are several methodological limitation of the studies which report a familiarity deficit – which contributed to the pooled familiarity deficit in the meta-analysis which are discussed in section 2.4. Whilst the limited power (Cohn et al., 2010) and ranging patient characteristics (Weierman et al., 2010; Davidson et al., 2006) may contribute to the suggestion of a familiarity deficit, it is most likely to be a result of the utilisation of the Process Dissociation Procedure (PDP, Jacoby, 1991). In this procedure, recollection estimates are derived from the exclusion condition as the frequency of endorsing intact target word pairs at recognition (a form of associative recognition as the test pair corresponds exactly to one presented during learning/encoding) in contrast to rejecting all other test pairs (new-new, rearranged old and half-old), specifically, rearranged pairs, both of which had been studied but not together. PDP assumes that a participant's ability to discriminate between intact and recombined word pairs to select only intact pairs must depend on recollection because it cannot depend on item

familiarity. However, it is known that associative familiarity can be found for several kinds of association, including those between words (Bastin Van der Linden, Schakers, Montaldi & Mayes, 2020; Harlow, MacKenzie & Donaldson, 2010). It is the contribution of associative familiarity, which suggests the levels of estimated recollection and item familiarity in the PDP may be seriously inaccurate given how the process dissociation equations work. This is because the simultaneous equations, related to the inclusion and exclusion conditions of PDP, cannot distinguish between the independent contributions of recollection, item familiarity and associative familiarity to a discrimination decision. Furthermore, possibly related to the above problem, the estimates of control recollection presented by Cohn et al., (2010) are surprisingly low. Estimates were not only similar to their PD cohort (resulting in the reported preserved recollection), but also to a group of mildly amnesic patients post unilateral medial temporal lobe resections in the treatment of temporal lobe epilepsy, as reported by Cohn et al., (2009). Assuming findings from the PDP are reliable, Cohn et al., (2010) suggest that the pattern of familiarity and recollection deficits are not simply a result of the brain structures affected by PD pathology, but that familiarity and recollection performance will vary as a result of the type of encoding. More specifically, however, they argued that the PD recollection deficit found following sentence generation suggests hippocampal dysfunction whereas the PD familiarity deficit following the reading of the word pairs was argued to reflect a PD strategic (organizational) and related attention deficit caused by striato-frontal dysfunction. There are serious problems with this proposal as there is considerable evidence that providing a good semantic elaborative encoding strategy improves recall in PD patients (e.g., VanSpaendonck et al., 1996; Knoke et al., 1998) similar effects have been noted where memory improves equally in amnesics and their controls, relative to a spontaneous encoding baseline condition (e.g., Mayes et al., 1980). Furthermore, even if PD familiarity was increased by giving sentence generation instructions (because it is not completely automatic), contrary to what Cohn et al. report, it would be expected to increase less, rather than more, than recollection, which is typically more effortful. Cohn et al. did not report any assessment of their patients' executive

functioning. It seems likely that, to the extent that they were typical PD patients, this would have been impaired and they and their controls would not have performed the sentence generation task in the same way and as a result, the patients' ability to follow the instructions properly would have been impaired, e.g., they may have produced sentences that did not improve recollection. Therefore, it is likely that suggestions of a familiarity deficit in PD is attributable to the use of the methodology used to derive familiarity and recollection estimates, rather than the accurate detection of a familiarity deficit in PD. This has implications for the interpretation of previous investigations into the status of recognition memory, familiarity and recollection in PD, or other populations, and to obtain reliable estimates of familiarity and recollection, the remember/know paradigm should be adopted and the recommendation from Migo et al., (2010) in implementing this paradigm should be followed.

The findings were also consistent with previous findings suggesting dopaminergic medication can impair recollection in PD (Edelstyn et al., 2010). In addition to this, findings revealed, for the first time that, specifically, pramipexole may induce a recollection impairment in PD, an effect not seen in a matched group of PD patients medicated with ropinirole. However, the indication of a dopaminergic medication induced recollection impairment has implications for how previous attempts to measure familiarity and recollection in PD can be interpreted, with all but Edelstyn et al., (2010) being tested in a medicated state and on a range of different dopaminergic medication combinations (Rodriguez et al., 2014; Algarabel et al., 2010; Weiermann et al., 2010; Cohn et al., 2010; Edelstyn et al., 2007; Davidson et al., 2006; Barnes et al., 2003; Hay et al., 2002). Furthermore, as illustrated by study 1 and the combination of study 1 and study 2 (phase 1 only), when exploring 'dopaminergic' effects on cognition, grouping patients who take different types of dopaminergic medication may not be the most rigorous methodology. When ropinirole and pramipexole subgroups are combined to make one PD cohort, no dopaminergic effects are found for familiarity or recollection estimates. It is only when the PD patients are allocated to subgroups on the basis of their dopaminergic agonist, and specific medication regimens are examined, that effects

were found, suggesting that the potential effect that pramipexole has on recollection in PD was being diluted when patients were combined with ropinirole patients, which appears to have no effect on recollection performance.

Previously, the focus of research assessing the effects of dopamine replacement therapy on cognition was on l-dopa and measures of prefrontal dependent executive functioning measures, which have showed dopamine repletion through l-dopa administration improves working memory (Cools, Myakawa, Sheridan & D'Esposito, 2010; Floel, Garraux, Xu, Breitenstein, Knecht, Herscovitch & Cohen, 2008; Mollion, Ventre-dominey, Dominey & Brousselle, 2003; Cools, Kulisevsky, Avila, Barbanoj, Antonijan, Berthier and Gironell, 1996), task switching (Cools, Barker, Sahakian & Robbins, 2003; Cools, Barker, Sahakian & Robbins 2001; Hayes, Davidson & Keele, 1998) verbal learning (Mattis, Tang, Ma & Eidelberg, 2011) planning (Hanna-Pladdy & Heilman, 2010; Cools, Stefanova, Barker, Robbins & Owen, 2002b) and attention (Fera, Nicoletti, Cerasa, Romeo, Gallo & Gioi, 2007). Alternatively, l-dopa administration impairs probabilistic reversal learning (Jahanshahi, Wilkinson, Gahir, Dharmarinda & Lagnado, 2010; Cools et al, 2001), decision making (Osman, Ryterska, Karimi, Tu, Obeso, Speekenbrink & Jahanshahi, 2014) impulsivity (Cools et al, 2003) and distractor resistance (Cools et al, 2010). As a result of this work, the dopamine overdose hypothesis (Gotham et al (1986) provided a robust theoretical framework for understanding the influence dopaminergic medication might have on cognition, including recognition memory. Although the dopamine overdose hypothesis may well account for how recognition memory may be effected solely by l-dopa, (although this is yet to be investigated), clinically, the vast majority of PD patient's medication regimens includes other agents effecting dopamine replacement, such as dopamine agonists. Edelstyn et al., (2010), provided evidence that the dopamine overdose hypothesis may be inadequate as according to the overdose model, in mild PD where dopamine depletion would be less severe, preserved familiarity and recollection estimates would be expected in OFF-medication conditions, but when ON-medication, medication induced impairments would be expected through an overdose effect. In moderate PD, recollection impairment would be expected when OFF-

medication as dopamine depletion is more severe, this impairment would therefore be remediated through dopaminergic treatment. However, as the opposite findings are reported in that dopamine treatment did not overdose and impair preserved familiarity and recollection in medicated mild PD. And medication failed to remediate recollection impairments in moderate PD and exacerbated impairment (Edelstyn et al 2010). The medication the patients were taking in Edelstyn et al's study were combining both types of dopamine agonists (and other agents), in the same group of PD patients. The dopamine overdose hypothesis, with its focus on l-dopa preparations would always be limited in how accurately it could explain the effect of dopaminergic medication on recognition memory once dopamine agonists are included in a patient's regimen as although l-dopa and dopamine agonists both stimulate dopamine receptors, they have contrasting pharmacokinetic characteristics, with l-dopa providing predominantly phasic dopaminergic stimulation and agonist providing a tonic dopaminergic stimulation (Poletti & Bonuccelli, 2013; Poewe et al 2010; Bonuccelli & Pavese, 2006). In addition to this, the different binding affinity for dopamine subreceptors of the individual agonists, a potential mechanism for understanding the pramipexole induced recollection deficit reported in study 1 of this thesis and in the combination analysis of study 1 and study 2 (phase 1 only), provided further limitation of the overdose hypothesis. The differences these modes of action have on cognition has been suggested by computation models of l-dopa and D2 agonists (Moustafa, Herzallah & Gluck, 2013) and in PD patients by Brusa et al.,(2003) who reported that pramipexole impaired, short term verbal memory, attention and executive function in a group mild PD patients, whereas l-dopa did not. The evidence presented in this thesis and existing literature have highlighted the inadequacy of the overdose hypothesis in understanding the dopaminergic mechanisms which underpin recognition memory. Whilst the work in this thesis has contributed to highlighting the inadequacy of the dopamine overdose hypothesis, as will the further work emanating from it, clearly much more work is required on dissociating the effect of not just l-dopa and dopamine agonists, but specific agonists too.

The evidence presented in this thesis has contributed to the wider dopamine modulation of hippocampal processes literature. With a growing body evidence supporting the importance of the the ventral tegmental area (VTA) and hippocampal loop, in hippocampal dependent episodic processes. Evidence from l-dopa administration versus placebo of healthy volunteers suggested that dopaminergic, post encoding consolidation process in the hippocampus occurs approximately 6 hours after learning (Chowdhury, et al., 2012). However dopaminergic medication administration in cognition studies in PD, including those presented in this thesis, have all taken place approximately within 1 hour after drug administration. The changes to prefrontal dependent function, discussed above, if assumed to reflect strategic memory processes, can be much more immediate (Miah et al., 2012; Cools et al., 2009; Brusa 2003). However, the findings from study 1, revealed no differences between pramipexole and ropinirole on prefrontal functions, whilst pramipexole seemed to induce a recollection impairment. Furthermore, the provision of strategic guidance at encoding and then at encoding *and* retrieval failed to remediate the recollection deficit found by Edeltyn et al., (2015). These findings suggest an important role for the dopaminergic regulation of learning in the hippocampus, independent of prefrontal dysfunction. Dopamine is involved in slow consolidation (6+ hours after encoding/learning), and therefore the pramipexole effect reported here may not be explained by a direct modulation by dopamine of encoding. However, there is preliminary evidence from rodent studies of an interaction between the D2 family of dopamine receptors and the N-methyl-D-aspartate (NMDA) receptors within the glutamatergic system, which plays an essential role in the synaptic plasticity in the hippocampus which is much more immediate. In fact, emerging evidence suggests that d3 subreceptor activity may control NMDA signalling (Solokoff, Leriche, Louvel & Pumain, 2013) and modulates long term depression, which may be one of a number of mechanisms by which dopamine replacement therapy and pramipexole in particular may indirectly negatively impact on encoding and short-retention memory (Solokoff, et al., 2013; Nakajima, Gerretson, Takeuchi, Caravaggio, Chow, Le Foll et al., 2013). Another potential mechanism by which pramipexole may impair recollection performance in the hippocampus is by inhibiting the

production of cAMP response element binding protein (CREB), which facilitates the synaptic plasticity for learning and memory. Activation of d3 subreceptors inhibits the production of adenylate cyclase and mitogen-activated protein kinase which regulates cellular gene expression of (CREB) (Yan, Feng, Fienberg & Greengard, 1999). A loss of CREB-dependent signalling in the rodent hippocampus has been associated with spatial memory impairment (Brightwell, Gallagher & Colombo, 2004) and the somatic gene transfer of CREB has been found to alleviate memory impairments in aged rats (Mouravlev, Dunning, Young & During, 2006). Rodent studies that have manipulated d3 subreceptor activation have provided further evidence which is complimentary to the evidence presented in this thesis. Xing, Meng, Wei and Li (2010) manipulated CREB production in a group of mutant mice with no d3 subreceptor expression and compared their performance on the Morris water maze task with a group of aged matched wild-type mice. The mutant mice exhibited a significantly improved performance compared to the controls on both the spatial learning and preceding memory test. Furthermore, the hippocampal CREB levels were significantly greater in the d3 subreceptor knockout mutant mice compared to the wild-type controls – no difference in CREB expression was found in prefrontal areas. Similarly, d3 subreceptor antagonist nafadotride has been shown to reduce scopolamine induced amnesia in rats (Sigala, Missale & Spano, 1997). Conversely, selective d3 subreceptor agonists induce amnesia in rats, an effect which is not be mediated by subsequent administration of d1 or d2 subreceptor antagonists (Ukai, Tanaka & Kameyama, 1997). It is therefore possible that through the inhibition of CREB production, pramipexole may impair recollection in PD, because of its high binding affinity for the d3 subreceptors which are prevalent in the hippocampus. The mechanism by which d3 subreceptor activation may impair recollection, the inhibition of CREB production and the d3 subreceptor mediation of glutamatergic and cholinergic dependent hippocampal functioning, particularly on long term depression, are presented here only as potential explanations and more work, ideally utilising imaging technologies, is required to elucidate these process in human participants. Furthermore, developing understanding of the interaction of dopaminergic, glutamatergic and cholinergic systems, specifically at the receptor level

of the hippocampus, is essential. Particularly in light of evidence that suggests the d3 activation effects on the glutamatergic innervation of the hippocampal system are not found on cholinergic innervation in the hippocampus, whilst d3 activation does modulate cholinergic innervation of the prefrontal cortex (see Nakajima et al., 2013 for full review). This has important implications for the understanding and therefore management of not just memory decline in PD and other clinical populations, but also of the aetiology and management of other nonmotor symptoms in PD.

Further work will be needed on the dopamine receptor reorganisation that occurs as a result of dopaminergic deafferentation in PD, or longer term dopamine replacement therapy use, (Flores, Manitt, Rodaros, Thompson, Rajabi Luk et al., 2005; Nitsch & Riesenberger, 1995). A limitation of the work presented here is that the duration of time PD patients had been taking their current dopamine agonist was not recorded. Therefore the impact of long term pramipexole use on d3 subreceptor activation and organisation compared to recently initiated pramipexole use or ropinirole cannot be determined or accounted for. Another limitation of the work presented here relates to omission of an impulsivity measure in the testing battery in both study 1 and study 2. Whilst the presence of an Impulse Control Disorder (ICD) was an exclusion criteria for both study 1 and study 2, impulsivity is a prevalent nonmotor symptom in PD (Zhang, Zhang, Liu, Yang Huang & Wang, 2014; Antonelli, Ray & Strafella, 2011). Furthermore, pramipexole use in particular has been associated with impulsivity in PD (Dodd, Klos, Bower, Geda, Josephs & Ahlskog, 2005; Driver-Dunkley, Samanta & Stacey, 2003). However, it is unlikely that the effect of pramipexole on recollection reported in this thesis is a result of impulsivity for two reasons. Firstly, it is unlikely that pramipexole was contributing to impulsivity in this group of PD patients, as the Hayling inhibition/suppression scores are comparable for PD patients and the HVs. Furthermore inhibition/suppression is comparable in the PD patients when they are medicated with ropinirole and pramipexole and when they are withdrawn from both drugs, as illustrated in Table 15. Secondly, impulsivity would lead to a more liberal response bias during the test phase of the recognition memory task and a significantly higher hit rate and false alarm rate would be expected in the PD

patients when medicated with pramipexole as opposed to when they are withdrawn, or medicated with ropinirole, or compared to the healthy controls, however, this is not the case as illustrated by the hit and false alarm rates presented in Table 14.

A further limitation of the work here relates to the small sample sizes of the PD and HV groups in study 1. The power analysis discussed in the Discussion section of Chapter 5, illustrated that in study 1, whilst no PD-dependent familiarity deficit was found but that this could be down to the limited power as a result of the small sample size. However, this seems to be unlikely as when participants from study 1 were combined to the participants of study 2, the observed power significantly increased but still no familiarity deficit was reported.

The mechanism by which recollection is suggested to impair recollection in PD in this thesis requires much further investigation. The link between the disruption of d3 subreceptors and the consequential memory impairment has been established using animal models of PD and this is the first programme of research to test this hypothesis in human subjects. PET studies could assay how dopaminergic activity is modulated by different medications when patients are engaged in recollection or recall activities, and determine whether this activity is correlated with patient recollection performance levels. Furthermore, the different binding profiles/activity in the hippocampus can be examined in much detail using PET and MRI scanning (similar to Takahasi et al., 2008), to greatly inform about the impact of D2 agonists on hippocampal functioning and the formation and inhibition of learning and memory processes.

Due to the acceptability and tolerability of pramipexole and ropinirole and the relatively short washout periods, the impact of pramipexole on recollection should be investigated in healthy control subjects (similar to how Chowdhury et al., (2012 administered low dosages of l-dopa in healthy subjects to explore slow consolidation in the hippocampus). A strength of adopting a methodology using healthy controls to investigate the effect of pramipexole on d3 subreceptors involved in hippocampal-dependent recollection processes is extraneous and putative factors arising

from the PD symptom complex are avoided. In addition, the short washout period of pramipexole, and ropinirole, would mean any negative impact on motor or nonmotor functioning in healthy controls would be transient.

The research presented in this thesis also has implications for the design of clinical trials in PD and has provided important insights into challenges of recruiting a target sample size. It was clear from the findings of study 3 that PD patients heavily rely on their routine medication and asking patients to switch medication as part of clinical investigation poses a great threat to their stability, which in turn compromises their capacity to complete their daily activities and quality of life. A genuine concern of both patients and their caregivers is that taking a drug, even if fully licensed, that they haven't taken previously, may not control their symptoms as well, or cause a deterioration of their condition that cannot be reversed. It is therefore of paramount importance for researchers designing clinical trials, to firstly ensure an accessible clinical support network is available whilst patients are involved with a trial, should they experience difficulties, and secondly that it is well advertised to patients and their caregivers and that contact details are available and clear in study documentation. Randomised controlled trials are essential to evidence-based clinical practice (Mathur et al., 2015) but the impact of clinical trial participation on a patient and their caregiver's quality of life, and the extra burden on the caregiver need to be considered. What is evident from study 3 of this thesis, is that the decision to take part in such trials is often not made solely by the patient, but involves input from the caregiver, and wider family members too. Therefore it remains a major challenge for study teams in the design stage, to consider the levels of burden a trial will have on the caregiver, not just the patient. As illustrated in the discussion section of chapter 4, in the design of a potential definitive trial of ropinirole and pramipexole, the number of testing sessions can be reduced with the removal of 1 OFF-medication testing session, which would dramatically attenuate participant burden. A further suggestion, for the design stage of trials, is to take the opinion of a Patient Participant Involvement (PPI) group, as their assessment on burden as a result of participation will be more accurate and realistic than the research team and will be a good predictor

of the likelihood an eligible patient will convert into a consent participant. Similar, a PPIE group can greatly inform the accessibility of the trial documentation. All study documentation, particularly invitation letters and patient information sheets, should be shown to a PPI group, with the opportunity for their assessments of accessibility and resulting feedback and suggestion incorporated prior to ethics submission.

A final implication is for the design stage of academic randomised controlled trials relates to how the study will be managed. The expertise of running trials by personnel, specifically trial managers, within Clinical Trial Units (CTU) can be an excellent resource and can have a wealth of experience in managing trials efficiently. However, managing a trial through a CTU, can often be more expensive than costing for staff from Research and Development department at trust sites which has implications for the development of the financial side of grant applications, which in turn has consequences for the selection of the funding stream that a research team may apply to. However, the expertise and resources that can be provided by a CTU, might suggest a better position for the efficient and timely delivery of clinical trials of investigational medicinal products.

As a result of the aging population, the number of people with PD is expected to rise. Expanding the knowledge and understanding of the complex, multifaceted symptom complex is essential. Nonmotor symptoms, are beginning to receive much more research attention, and evidence has shown just how important they are in impacting on a patient's and their caregiver's quality of life (Schrage et al., 2000). If a particular type of PD medication, in this case pramipexole, which is particularly effective in alleviating depressive or tremor based symptoms, but may cause, or at least contribute to a memory disorder in PD, has huge implication for choices pertaining to clinical management of PD symptoms and the education of PD patients and their caregivers. Until study 1 of this thesis, understanding the cognitive effects of agonists, especially pramipexole were limited to measuring its effects on working memory and verbal memory (Costa, 2009; Cools et al., 2006; Brusa

et al., 2003). A clinical scenario of PD patients who present with depressive or tremor dominant symptoms, may need extra support for a potential memory decline as a result of the most effective treatment, in pramipexole. Similarly, a joint clinical decision by the treating physician and patient about whether motor symptoms, mood symptoms or preserving memory status are a priority for treatment is a potential clinical decision based on the findings suggested by study 1 of this thesis.

Evidence of Mild Cognitive Impairment (MCI) being a precursor to dementia is well established (Busse, Matthia, Angermayer, Steffi & Riedel-Helle, 2006). However, with assessments of PD patient's cognitive status typically being completed in a medicated state, the impact that dopaminergic medication has on that status has largely been ignored. Evidence from Edelstyn et al., (2010) and the result of the work presented here might suggest that estimated numbers of MCI in PD, and the conversion to a full dementia diagnosis, may need to account for the dopaminergic medication effects to ensure that prevalence estimates are accurate. Furthermore the medication that PD patients currently take need to be taken in to account when developing individualised care plans.

Ultimately, a long term aim of the type research presented in this thesis should be to contribute to clinical guidelines, informing clinical decision making when medicating PD patients. Specifically, whether particular PD phenotypes, who may present in a certain way in clinic, who may be particularly vulnerable to memory impairment if medicated with a particular dopamine agonist, could be treated in a way to avoid this. Any idea of being able to assess recollective or episodic memory in a clinical setting using a measure based on the remember/know paradigm seems unlikely, due to its complexity, dependency on both participant and administrators understanding of the procedure and the length of time it takes to complete (for a review, see Migo et al, 2012). Therefore immediate recall may be a more clinically relevant and accessible way of assessing memory status in PD patients in a clinical setting. However, the sample size calculation conducted on the data collected from the work presented here, suggests a much greater sample size would be

required for a definitive trial, than for recollection. This in turn has implications for the design of and resources required for a much larger trial.

Further research is most definitely warranted in identifying potential phenotypes or subgroups within the initial diagnosis of PD. Whilst the majority of work has focused on using motor symptoms (Lewis et al 2005; Tenganalt et al., 2014) to cluster patients into potential groups, the omission of nonmotor symptoms is a clear limitation of those studies. The importance of including such symptoms in identifying phenotypes is paramount as illustrated by Tremblay, Achim, Macoir and Monetta (2013) with the MMSE and Alzahrani and Venneri (2015) who reported on the connections between nonmotor symptoms, where executive functioning deficits were present in PD patients with depression, apathy, anxiety and visual hallucinations, whereas memory disorder was predominantly associated with depression and visual hallucinations. The long term goal of accurately identifying phenotypes which encompass a broader range of the motor and nonmotor symptoms will be to develop a way to select a medication regimen, or other treatment options that specifically supports that set of symptoms.

Although dopamine depletion is the primary deficit in PD, multiple neurotransmitter systems such as acetylcholine, noradrenaline and serotonin, which are interlinked, are also disturbed (Fox 2014; Lang & Obeso, 2004). Whilst this is beyond the scope of the work completed in this thesis an ultimate objective for research, particularly with advancing imaging technologies, should be to understand their complex relationship which may illuminate the aetiology of the nonmotor symptoms of PD, not just memory disorder (Benarroch, 2012).

In closing, the research programme presented in this thesis is by no means a conclusive piece of research, but has provided the first step in the exploration of how dopamine agonists, specifically pramipexole may contribute to memory disorder in PD. It has also provided a clear pathway of future investigation based on empirical findings and the piloting of an innovative design. It has provided a rationale for further, more specific research into the effects of dopaminergic

agonists and their potential interaction with hippocampal functioning and resulting impact on memory disorder in PD. Future research, directed by the work presented in this thesis has the potential to contribute to guidelines informing the clinical management of PD as well as bridging a relationship with academic literature relating to the status of recognition memory in PD, dopaminergic systems and the hippocampal versus prefrontal theories of recollection decline in PD. It has also provided evidenced based recommendations for the design and management of future clinical trials, the relevance of which may extend further than trials involving PD patients.

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Appendix A



K E E L E
UNIVERSITY

ACADEMIC SERVICES DIRECTORATE
RESEARCH AND ENTERPRISE SERVICES

7 February 2011

Mr T Shepherd
PhD Student – Psychology
Room DH0.66
Dorothy Hodgkin Building

Dear Tom

EXPLORING THE EFFECTS OF DOPAMINERGIC MEDICATION ON MEMORY IN PARKINSON'S

The above project has received final approval from the Independent Peer Review Committee and is permitted to progress for ethical review. Please find attached the peer review comments and accompanying letter for the above project. LREC requests that all peer review proforma/s are sent along with your LREC application form.

Although this project has been deemed appropriate based on scientific merit, you may wish to incorporate the reviewer's constructive comments to strengthen your protocol.

Management approval

You should arrange for all relevant NHS care organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant care organisation before commencing any research procedures. Where a substantive contract is not held with the care organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Clinical trial of a medicinal product

Please remember that, if your project is a clinical trial of a medicinal product, MHRA approval is required. You must submit a request for a clinical trial authorisation under the Medicines for Human Use (Clinical Trials) Regulations 2004. Further details can be found at <http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2022633.pdf>

If you have any queries, please do not hesitate to contact Nicola Leighton on 01782 733306.

Yours sincerely

Professor Shaun O'Brien
Chair – Independent Peer Review Committee

CC

Dr Darren Clement, R&D Dept, UHNS



Keele University
Peer Review Proforma
Annex A
For Honors and Further Education

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PEER REVIEWER'S PROFORMA (Reviewer 1)

Research Project Details	
Project title	Exploring the effects of dopaminergic medication on memory in Parkinson's
Name of principal investigator	Thomas Shepherd
Institution of principal investigator	Student – Keele University

The important or relevance of the problem to be addressed in relation to either or both of:

- a) The particular field of research as a whole
The question of how memory is affected by medication in Parkinson's disease is an important topic for the field of cognition and Parkinson's disease. The project has the potential to make an important theoretical contribution.
- b) The value of this research for health or social care
The findings of this study could inform medication choice for individual patients, leading to an improved quality of life.

The quality and relevance of the background information provided

The background to the project is well presented covering the prevalence of Parkinson's disease, the wide use of D2 agonists and the issue of memory in Parkinson's disease.

Design, methods and strengths and weakness of the proposed plan of investigation

This project uses a cross-over design to compare and contrast the effect of Ropinerole and Pramipexole – patients will be tested on and off their routine medication, before being crossed over to the opposite D2 agonist and again being tested on and off medication following a 6-week stabilisation period. The main measure will be a memory test of recollection and familiarity, but they will also assess related measures of vigilance, depression and sleepiness, as well as their self-reported quality of life and incidence of everyday memory problems. The design is highly appropriate and the measures are well thought out.

My only concern is about the rate of recruitment to the study and possible difficulty in getting enough participants for phase 2.

Appropriateness of resource requirements

The project is being supported by a charity. The level of funding was not specified, however, the main cost will be the PhD student's time.

General feedback (indicate major areas where changes will be required, indicate whether any weaknesses indicated in any of the above categories are major or minor areas of concern)

Major concerns – none

Minor concerns – some clarification of the following may help the project at the point of ethical review:

- Give some estimate about rates of recruitment of patients to the study
- Indicate whether patients will be able to time the 6 week change of medication to suit their life demands.
- Indicate whether patients could be advised or allowed to remain on the experimental D2 agonist if this suited them better.
- Level of financial support not specified
- it might be useful to include a Parkinson's disease nurse in the steering group

Assessment of Merit

Grading	Description	Please tick
1	Proceed without any revision. Project may be submitted for appropriate NHS/University approval and then to either the Local or the Multi-Centre Research Ethics Committee.	
2	Minor amendments or Further information required. Revise project according to reviewer(s) recommendations. Document to be checked by Internal Committee Member prior to Chairman's approval to proceed.	x
3	Complete major revision required. Principal Investigator to discuss outcome with Centre/Programme Director and agree plan to complete substantive revision of the project (with support as agreed). Resubmission will need to be reviewed and approved by Internal Committee Member, prior to Chairman's approval to proceed.	
4	Reject on the basis that the project has major scientific flaws	

The terms on and off are confusing as most commonly in PD they refer to clinical states of motor activity rather than whether on a particular medication or not.

Summary of Study: I found this a little difficult to follow. For Phase I it is stated that there will be no change in medication regime. I assume what is meant here is that there will be no change in regime except for delayed administration of the D2 agonists whilst the off stage is assessed. Will patients have to have been on this medication for a certain period of time before entering the study?

Phase II. How is dosage to be determined and how will drugs be titrated, if they are to be titrated at all. Is there evidence for the 6 week stabilisation time period?

I am not sure what counter-balanced means. Does it mean that 50% will be assessed in an off state first and 50% in an on state? Will this be in the same order in Phase II?

A chart indicating at which time points the individual tests will be undertaken would be helpful. For example will the PDQ-39 be administered just once and what is going to be the time interval between this and entry into the study.

Study Population: Are all patients taking one or other of these drugs in the clinics to be screened for entry into the trial? It is important to know how representative the patient sample is of all patients taking these drugs and this will be a problem relating to those attending groups. How will matching be undertaken? How is IQ to be measured? People attending U3A are likely to be different to patients in many ways other than just not having Parkinsons..

Treatment interventions: The assumption is that pharmacokinetic changes relate directly to pharmacodynamic changes in cognition. Is there evidence for this? Is the period "off" the medication long enough to detect any change? Do you know whether in all cases the D2 agonist is clinically effective? If it is not then a longer "off" phase may be justified.

My reading is that this is an open label study. Is there any blinding? Is the study nurse or the applicant going to do some/all of the tests? Is any attempt going to be made to avoid observer bias?

If the research presents ethical concerns, does the plan of investigation/scientific background address these concerns? NB - The final decision about ethics rests with the Local Research Ethics Committee

I can see no specific ethics issues.

PEER REVIEWER'S PROFORMA (Reviewer 3)

Research Project Details	
Project title	Exploring the effects of dopaminergic medication on memory in Parkinson's
Name of principal investigator	Thomas Shepherd
Institution of principal investigator	Student – Keele University

The important or relevance of the problem to be addressed in relation to either or both of:

- c) The particular field of research as a whole

This is a timely study into an under-researched area of Parkinson's.

- d) The value of this research for health or social care

To be commented on by other reviewer, but obvious implications for improvements in patient care management.

The quality and relevance of the background information provided

This is a well written and thorough section with only some minor typographical errors for amendment. I have done 'track changes' on the original document and include that with this review.

Design, methods and strengths and weakness of the proposed plan of investigation

Again there are typographical errors and one or two issues of clarification (e.g., who is meant by the 'neuropsychology health volunteer panel' referred to on page 7) which need to be addressed and these are documented via track changes as above.

Additionally, there are 5 main methodological issues which need to be addressed, but these are relatively minor:

1. On page 8 it states that there will be a retention interval of 20 minutes between study and test during which time the cognitive test battery will be administered, yet the timings presented for this add up to 29 minutes.
2. Regarding the recognition memory task on page 8. It is unclear whether a one-step or two-step procedure is being used for this task and this needs to be clarified.
3. Can you say a little about the instructions that are to be used for the recognition task as these can be quite complex and may impact on the patient's understanding. Presumably the order of presentation of the recognition task stimuli will be randomised for each patient/participant?

General feedback (indicate major areas where changes will be required, indicate whether any weaknesses indicated in any of the above categories are major or minor areas of concern)

Apart from general typographical errors (detailed in track changes), the main changes needed are to the methods section. These changes are minor areas of concern in that I think they warrant attending to, but they are procedural rather than fundamental.

Assessment of Merit

Grading	Description	Please tick
1	Proceed without any revision. Project may be submitted for appropriate NHS/University approval and then to either the Local or the Multi-Centre Research Ethics Committee.	
2	Minor amendments or Further information required. Revise project according to reviewer(s) recommendations. Document to be checked by Internal Committee Member prior to Chairman's approval to proceed.	X
3	Complete major revision required. Principal Investigator to discuss outcome with Centre/Programme Director and agree plan to complete substantive revision of the project (with support as agreed). Resubmission will need to be reviewed and approved by Internal Committee Member, prior to Chairman's approval to proceed.	
4	Reject on the basis that the project has major scientific flaws	

Appendix B

Health Research Authority

NRES Committee West Midlands - Staffordshire

Prospect House
Fishing Line Road
Redditch
Worcestershire
B97 6EW
Tel: 01527 582535
Fax: 01527 582540

07 December 2011

Mr Thomas Shepherd
PhD student (Chief Investigator)
Keele University
School of Psychology
Staffordshire
ST5 5BG

Dear Mr Shepherd

Study title: Exploring the effect dopaminergic medication and recognition memory in Parkinson's.
REC reference: 11/WM/0119

Amendment number: AM01 (our ref)
Amendment date: 23 November 2011

The above amendment was reviewed on 07 December 2011 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Information Sheet: DA patient information sheet	3	25 November 2011
Protocol Changes	1	25 November 2011
Notice of Substantial Amendment (non-CTIMPs)		23 November 2011
Covering Letter		24 November 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/WM/0119:	Please quote this number on all correspondence
-------------	--

Yours sincerely



 **Dr Kathryn Kinmond**
Chair

E-mail: Jenny.Tyers@westmidlands.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs Nicola Leighton*
 Dr Darren Clement, University Hospital of North Staffordshire

Health Research Authority

NRES Committee West Midlands - Staffordshire

Sub-Committee of the REC meeting on 07 December 2011 in correspondence

<i>Name</i>	<i>Profession</i>	<i>Capacity</i>
Dr Kathryn Kinmond	Senior Lecturer	Lay Plus
Dr Sandie Sandbrook	Senior Lecturer	Expert
Mr Victor Scofield	Legal Advisor, Banking (Retired)	Lay Plus

Appendix C



Dear

You are being invited to consider taking part in a study organised jointly by the University Hospital of North Staffordshire and Keele University.

Our study is investigating memory in patients with Parkinson's Disease.

The enclosed *Information Sheet* outlines the study and what participation in it will entail.

You are free to decide whether you would like to participate or not. If you do decide to take part, please complete the response slip below and return it to Mr Tom Shepherd in the stamped addressed envelope within the next 14 days.

If you do not want to participate, you can either return the opt-in slip having ticked the second option, or you don't need to get back in touch with us all. However, we will be sending out one reminder letter in 10 days to everyone who hasn't returned the response slip – just in case the original letter and study documentation has been lost. So, we apologise in advance if you receive this reminder letter when you have already decided not to participate but haven't got back in touch with us

Kind regards,

Dr SJ Ellis	Dr Nicky Edelstyn	Mr Thomas Shepherd
Consultant Neurologist	Senior Lecturer	PhD Student



Response slip

- ☐ I am interested in taking part.
- ☐ I am not interested in taking part.

Name:
Print Signature Date

Please indicate your preferred contact details if you are opting into the study.

Email address:

Telephone number:

If you prefer contact by telephone, please indicate times when it's best for us to call you.



Dopamine Agonist Patient Information Sheet

Study Title: Dopaminergic medication and recognition memory in Parkinson's

Invitation

You are being invited to consider taking part in a research study investigating memory in Parkinson's disease. This project is being jointly undertaken by Dr Simon Ellis, Consultant Neurologist, Department of Neurology, University Hospital of North Staffordshire Mr Thomas Shepherd PhD student, Keele University and Dr Nicky Edelstyn, Senior Lecturer, Keele University.

Before you decide, it is important for you to understand why this research is being done and what it will involve. Please take time to read this leaflet carefully and discuss it with friends and **relatives** if you wish. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part and discuss this with your carer or **relatives**.

What is the study about?

A lesser-known aspect of Parkinson's disease is memory impairment. Although worrying about memory loss may seem trivial in comparison to the marked movement abnormalities which characterise the condition, memory deficits can have far reaching consequences. For example, difficulties recognising new acquaintances and remembering recent events can lead to self-consciousness, avoidance of social situations and



consequently, social isolation and depression. The ability to relive past experiences is called “recognition memory” and it is this type of memory which is particularly affected by Parkinson’s.

In a recent study we found that the drugs used to control the motor symptoms of Parkinson’s also affect recognition memory – some drugs appear to make the memory impairment worse, whilst others can remediate the memory decline and make it close to normal. However, only small numbers of patients participated in this study, and we now want to re-run the study using much larger numbers of patients. By recruiting many more patients we can find out if our earlier findings were just specific to those patients or are generally representative of Parkinson’s.

Why have I been chosen?

Patients in our earlier study were on a variety of different medication regimens which included a dopamine D2 agonist (either ropinirole, pramipexole), which may or may not have been combined with L-dopa. We also had patients on L-dopa without a dopamine agonist.

In this study we want to study the separate effects of ropinirole, pramipexole and rotigotine (with or without L-dopa) on memory in Parkinson’s. Because you are taking ropinirole, pramipexole or rotigotine (with or without L-dopa), **we would like you to consider being part of our dopamine agonist group.**

Do I have to take part?

You are free to decide if you wish to take part or not. If you do decide to take part you will be asked to sign two consent forms, one is for you to keep and the other is for our records. You are free to withdraw from this study



at any time and without giving reason. This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future.

What will happen if I take part?

The study involves 1 screening visit with Dr Simon Ellis, Consultant Neurologist at a research-dedicated outpatient clinic in the Department of Neurology, University Hospital of Neurology and 3 research sessions which will take place in your home.

For 1 of these research sessions you will take your medication as normal (which we will call ON or medicated session). For the other research session you will be required to be in an unmedicated state (which we will call OFF). The instructions on how to with hold your medication and which medications should be withheld will be described in the screening visit by Dr Ellis. Dr Ellis will also describe how to restart taking your medication after the research session has finished. All the instructions will be written down for you on a *study card* which you can take away with you.

The unmedicated research sessions will show us what effect Parkinson's has had on your memory, whilst the medicated sessions will tell us about the additional effects of your medication on memory. The third session will be an interview where you will be asked questions about your memory and how it affects you. You will take your medication as normal for this interview session.



Because memory varies during the day - usually it is better in the morning when less fatigued by the day's activities, all groups will be tested between 9.00am-10am.

The first 2 research session will take approximately one hour and the interview session will take approximately 30 minutes.

The timetable for the screening and research visits is detailed as follows:

Week 1: Screening visit.

Weeks 2-3: Research sessions 1 and 2: For one of these sessions you will be medicated and for the other unmedicated. The order of medicated and unmedicated research sessions will vary.

Week 4: The interview session.

More details about what will happen during the screening visit and each of the research sessions are detailed below.

Screening visit

Dr Ellis will discuss the study with you and explain the effects of delaying your first medication of the day in preparation for the unmedicated research session. If you already experience motor stiffness in the morning before you take your first medication for example, delaying your medication will prolong the period of motor stiffness until you take your morning medication.



Dr Ellis will refer to your medical notes (once you have given him permission to do this during the screening visit) to check your current medication regimen. He will inform you which of the drug/s you are currently taking to delay on the morning of the 'off' research session. He will also write this information on a *Study Card* to help you remember which drugs are to be delayed. The *Study Card* will also have other important information such as the contact number of the Parkinson's nurses should you wish to contact them during the study and the dates and times of the 'OFF' and 'ON' research sessions, and end of study visit.

The unmedicated research session will be arranged for anytime after 8.30am on a day to suit you. This research session will take approximately 60 minutes (depending on length and frequency of breaks required), the delayed drug/s **MUST** be taken as soon as the testing is completed. It is **VERY IMPORTANT** that only the drug/s indicated by Dr Ellis should be delayed.

Dr Ellis will also go through the study exclusion criteria with you. Unfortunately, if you answer 'yes' to any of the following: if you or a close relative (parent, sibling) have a psychiatric illness, such as schizophrenia or major depression; a neurological history of epilepsy, major head injury (loss of consciousness for more than 6 hours); if you have a learning difficulty or dyslexia; history of substance abuse such as alcoholism; significant cognitive decline within 12 months of motor symptom onset; taking COMT inhibitors, anticholinergics; history of hallucinations or dyskinesias; English is a second language; or minimal score of less than 26 we can't include you in this study.

Once you have had all of your questions answered by Dr Ellis and Mr Thomas Shepherd at the screening visit, you can decide whether to enter the study. If you do decide to take part Mr Tom Shepherd who is responsible



for running the study will phone you within the next couple of days to arrange the dates for the 2 research sessions and the interview session. Or, if you bring your diary along appointments can be arranged at the screening visit. Your travel expenses to the hospital for this screening visit and the end of study visit will be reimbursed (45p per mile plus parking if you drive or are driven). We can also cover taxi-fares with a receipt. Dr Ellis will then send a letter to your GP to inform them about the nature of your participation.

Research Sessions

It is important that each research session takes place at the same time of day. And since memory is generally best in the morning, and, we don't want to unnecessarily prolong the delay in taking your medication in preparation for the unmedicated research sessions, we will aim to start each research session around 9.00 or 9.30am in the morning.

During the first 2 research sessions we will be using the same type of test to examine your memory for words (although the items to remember will be different). The memory tests involve a study phase where we'll present 50 words, one at a time. There will be a short delay, and then we'll test your memory for the words you've just studied, we'll call them targets. This will be done by mixing up the target words with words you haven't seen before and your job will be to pick out the targets from the new words.

In addition to this recognition test, we'll also be asking you to complete:

- A test of memory and attention;
- 5 questionnaires which assess the impact of Parkinson's' on your daily activities (*Parkinson's Disease Questionnaire*), and the effect of Parkinson's on your day to day memory (*Test of Everyday Memory*),



mood (*Hamilton Depression Inventory*) and if you experience daytime sleepiness (*Daytime Sleepiness Questionnaires*);

- 2 assessments of disease and symptom severity (Hoehn and Yahr disease severity rating scale, and the motor subsection of the *Unified Parkinson's Disease Rating Scale*).

Whilst all of this seems like quite a lot to do in 60 minutes, the questionnaires and disease severity rating scales are short, and take only a couple of minutes each to complete. There will be lots of opportunity to take breaks, and we can stop the research session at any point if you feel too fatigued to carry on. The interview session will be approximately 30 minutes long and will be an opportunity to discuss how you feel about your memory, and how you feel your memory affects your day to day life and daily activities.

It's important for you to know that we have had experience of working with Parkinson's patients when unmedicated – these patients were at a variety of severity stages of the illness – and they told us that the unmedicated research session was manageable and that their experience of it wouldn't put them off participating in future studies which required them to delay their medication again.

What do I have to do?

If you wish to find out more about the study please return the response slip (attached to the covering letter) in the stamped addressed envelope. We will send you a reminder letter just in case you're interested but have lost the response slip. We won't send anymore reminders. If you don't want to take part in this study, you can either return the response slip telling us so or do nothing. However, we will be sending out reminder letters to everyone we haven't heard from.



What are the benefits of taking part?

There are no expected benefits to you personally. However, this study will provide a greater understanding of the effects of different types of anti-Parkinsonian medication on memory in Parkinson's. This knowledge will influence decisions about medication management for patients with Parkinson's.

What if something goes wrong?

We don't expect any problems to arise in this study. If you are harmed by agreeing to take part in this research, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of the study, you may address this to Professor Michael Murray, Research Director, School of Psychology, University of Keele, Keele, Staffordshire ST5 5BG.

Will my taking part be kept confidential?

All of the research data that we collect during the study will be kept strictly confidential. Any information which has your name, address and any other identifying information will be kept in a locked filing cabinet in the School of Psychology. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name.



Research Office
Department of Neurology
University Hospital of North Staffordshire
Princes Road
Hartshill
Stoke-on-Trent
Staffordshire
ST4 7LN

Tel/Fax: 01782 555008

Who is organizing the research?

Dr Simon Ellis and Dr Nicky Edelstyn have organised the study. Mr Tom Shepherd will coordinate and run the research sessions.

Contact for further information

Mr Tom Shepherd

01782 734402 or 07841647240

t.a.shepherd@ilcs.keele.ac.uk

School of Psychology, Keele University

Dr Nicola Edelstyn

01782 734398

n.edelstyn@psy.keele.ac.uk

School of Psychology, Keele University

One copy of information sheet to be retained by the participant.



K E E L E
U N I V E R S I T Y

Keele Neuropsychology Parkinson's Research Group,
School of Psychology,
Keele University,
Keele,
Staffordshire ST5 5BG.
February 1st, 2011.

Dear

You are being invited to consider taking part in a study organised jointly by the University Hospital of North Staffordshire and Keele University.

Our study is investigating memory in patients with Parkinson's Disease.

The enclosed *Information Sheet* outlines the study and what participation in it will entail.

You are free to decide whether you would like to participate or not. If you do decide to take part, please complete the response slip below and return it to Dr Nicky Edelstyn in the stamped addressed envelope.

If you do not want to participate, you can either return the opt-in slip having ticked the second option, or you don't need to get back in touch with us all. However, we will be sending out one reminder letter in 14 days to everyone who hasn't returned the response slip – just in case the original letter and study documentation has been lost. So, we apologise in advance if you receive this reminder letter when you have already decided not to participate but haven't got back in touch with us

Kind regards,

Dr SJ Ellis

Dr Nicky Edelstyn

Mr Tom Shepherd

Consultant Neurologist

Senior Lecturer

PhD student



KEELE
UNIVERSITY

Response slip

- ☐ I am interested in taking part.
- ☐ I am not interested in taking part.

Name:

Print

Signature

Date

Please indicate your preferred contact details if you are opting into the study.

Email address:

Telephone number:

If you prefer contact by telephone, do you have preferred times?



KEELE
UNIVERSITY
MEDICAL SCHOOL





K E E L E
U N I V E R S I T Y

Keele Neuropsychology Parkinson's Research Group,
School of Psychology,
Keele University,
Keele,
Staffordshire ST5 5BG.

March 1st, 2011.

Dear <Insert participant's name>,

We recently sent you an information pack detailing a study we are conducting in North Staffordshire, investigating the effect of Parkinson's Disease on memory.

We haven't heard from you and are therefore sending this reminder letter along with the same study documentation just in case you are interested but haven't got round to letting us know.

This is the only reminder letter we'll be sending, so if we don't hear from you we understand that you don't want to take part.

Best wishes,

Mr Tom Shepherd

Dr SJ Ellis

Dr Nicky Edelstyn



K E E L E
U N I V E R S I T Y

Response slip

- ☐ I am interested in taking part.
- ☐ I am not interested in taking part.

Name:
Print Signature Date

Please indicate your preferred contact details if you are opting into the study.

Email address:

Telephone number:

If you prefer contact by telephone, please indicate times when it's best for us to call you.

Email address:.....



Keele Neuropsychology Parkinson's Research Group,
School of Psychology,
Keele University,
Keele,
Staffordshire ST5 5BG.

Healthy Volunteer Information Sheet

Study Title: Dopaminergic medication and recognition memory in Parkinson's

Invitation

You are being invited to consider taking part in a research study investigating memory in Parkinson's disease. This project is being jointly undertaken by Dr Simon Ellis, Consultant Neurologist, Department of Neurology, University Hospital of North Staffordshire, Tom Shepherd, Keele University and Dr Nicky Edelstyn, Senior Lecturer, Keele University.

Before you decide, it is important for you to understand why this research is being done and what it will involve. Please take time to read this leaflet carefully and discuss it with friends and **relatives** if you wish. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part and discuss this with your **relatives**.

What is the study about?

A lesser-known aspect of Parkinson's disease is memory impairment. Although worrying about memory loss may seem trivial in comparison to the marked movement abnormalities which characterise the condition, memory deficits can have far reaching consequences. For example, difficulties recognising new acquaintances and remembering recent events can lead to self-consciousness, avoidance of social situations and consequently, social isolation and depression. The ability to relive past experiences is called "episodic memory" and it is this type of memory which is particularly affected by Parkinson's.

In a recent study we found that the drugs used to control the motor symptoms of Parkinson's also affect recognition memory – some drugs appear to make the memory impairment worse, whilst others can remediate



the memory decline and make it close to normal. However, only small numbers of patients participated in this study, and we now want to re-run the study using much larger numbers of patients. By recruiting many more patients we can find out if our earlier findings were just specific to those patients or are generally representative of Parkinson's.

Why have I been chosen?

In order for us to understand the nature and extent of medication-dependent memory change in mild Parkinson's, we need to examine the *same* memory processes in healthy individuals who do **not** have Parkinson's disease and are of a similar age and educational background to the patients.

We would like you to consider being part of our healthy volunteer group.

Do I have to take part?

You are free to decide if you wish to take part or not. If you do decide to take part you will be asked to sign two consent forms, one is for you to keep and the other is for our records. You are free to withdraw from this study at any time and without giving reason. This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future.

What will happen if I take part?

If you are interested in participating in this study, please return the response slip in the stamped-addressed envelope. You will then be contacted to arrange an appointment in the School of Psychology, University of Keele, to discuss the study further and have any questions you may have answered. At this visit, Mr Tom shepherd who is running the study will go through the study exclusion criteria with you. Unfortunately, if you answer 'yes' to any of the following: if you or a close relative (parent, sibling) have a psychiatric illness, such as schizophrenia or major depression; a neurological history of epilepsy, major head injury (loss of consciousness for more than 6 hours); if you have a learning difficulty, dyslexia, or history of substance abuse such as alcoholism, we can't include you in this study.

If you are eligible and willing to take part, your consent to participate will be taken at this first research visit. In addition to this first visit, we will need to see you on **ONE** further occasions in order to complete our

measures of memory, attention, and questionnaires about daytime sleepiness and mood. It is estimated that each research session will last one hour. If you wear reading glasses please **bring them** along.

It is estimated that the duration of your involvement in this research will be 2 weeks. The 2 research sessions can take place in the same week if you prefer. Each research sessions will take place in the morning either in the School of Psychology, Keele University or at your home if preferred. You will be paid £5 per research session, and have your travel costs reimbursed (40p per mile plus parking).

What do I have to do?

If you wish to find out more about the study please return the response slip (attached to the covering letter) in the stamped addressed envelope. We will send you a reminder letter just in case you're interested but have lost the response slip. We won't send anymore reminders. If you don't want to take part in this study, you can either return the response slip telling us so or do nothing. However, we will be sending out reminder letters to everyone we haven't heard from.

What are the benefits of taking part?

There are no expected benefits to you personally. However, this study will provide a greater understanding of the effects of different types of anti-Parkinsonian medication on memory in Parkinson's. This knowledge will influence decisions about medication management for patients with Parkinson's.

What if something goes wrong?

We don't expect any problems to arise in this study. If you are harmed by agreeing to take part in this research, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of the study, you may address this to Professor Michael Murray, Research Director, School of Psychology, University of Keele, Keele, Staffordshire ST5 5BG.

Will my taking part be kept confidential?

All of the research data that we collect during the study will be kept strictly confidential. Any information which has your name, address and any other identifying information will be kept in a locked filing cabinet in the School of Psychology. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name.

Who is organizing the research?

The research is being organized and ran by Mr Tom Shepherd, Dr Nicky Edelstyn and Dr Simon Ellis.

Contact for further information

Mr Tom Shepherd

Telephone: 01782 734402

Email: t.a.shepherd@ilcs.keele.ac.uk

School of Psychology, Keele University

Dr Nicky Edelstyn

Telephone: 01782 734398

Email: n.edelstyn@psy.keele.ac.uk

School of Psychology, Keele University

One copy to be retained by participant



K E E L E
U N I V E R S I T Y

Research Office
Department of Neurology

University Hospital of North Staffordshire
Princes Road, Hartshill
Stoke-on-Trent
Staffordshire
ST4 7LN

Tel/Fax: 01782 555008
November 1st, 2011

Dear Dr. <insert GP'S NAME>

Re: <insert PATIENT'S NAME>

The above named patient has kindly agreed to participate in our research study looking at the effects of D2 dopamine agonists on memory in Parkinson's. This is a collaborative project with Dr Nicky Edelstyn (senior lecturer in cognitive neuroscience, School of Psychology, Keele University) and funded by Parkinson's UK.

Your patient will be participating in our study for approximately 3-4 weeks, during this time s/he <delete as appropriate> will have his/her memory tested once in his/her normal medicated state and once on another time following a withdrawal period when s/he <delete as appropriate> will refrain from taking her/his routine dopaminergic medication <insert details>.

I have already met with your patient and reviewed her/his <delete as appropriate> medical notes, and written down on a study card for her/him <delete as appropriate> which medication is to be withheld in preparation for the OFF-medication session, and provided emergency contact details should s/he <delete as appropriate> require urgent medical attention during this time.

After these 2 research sessions (ON and OFF) s/he will take part in an interview regarding memory and day to day activities.

Please don't hesitate to get in touch if you require further information.

Yours sincerely,

Dictated but not signed by

Dr SIMON J ELLIS
Consultant Neurologist



Research Office

Department of Neurology

University Hospital of North Staffordshire
Princes Road
Hartshill
Stoke-on-Trent
Staffordshire
ST4 7LN

Tel/Fax: 01782 555008

March 1st, 2011

Dear **(PATIENT'S NAME)**,

Two weeks ago we sent you information about a study we are conducting in North Staffordshire, which is investigating the effect of Parkinson's medication on memory.

We haven't heard from you and are therefore sending this reminder letter along with the same study documentation just in case you are interested but haven't got round to letting us know.

This is the only reminder letter we'll be sending, so if we don't hear from you we understand that you don't want to take part.

Best wishes,

Mr Tom Shepherd

Dr SJ Ellis

Dr Nicky Edelstyn



Response slip

I am interested in taking part.

Name:

Print

Signature

Date

Telephone number:.....

Email address.....





K E E L E
UNIVERSITY

Research Office
Department of Neurology
University Hospital of North Staffordshire
Princes Road
Hartshill
Stoke-on-Trent
Staffordshire
ST4 7LN
Tel/Fax: 01782 555008
March 1st, 2012

PATIENT CONSENT FORM

Study Title: Dopaminergic medication and recognition memory in Parkinson's

Investigators: Dr Simon Ellis, Mr Tom Shepherd, and Dr Nicky Edelstyn

Please initial box

- 1 I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.
- 2 I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3 I understand that data collected about me during this study will be anonymised before it is submitted for publication in a scientific journal.
- 4 I give permission to authorized individuals to look at my medical notes and data where it is relevant to my taking part in this research project.
- 5 I agree to take part in the 2 research sessions of this study.
- 6 I agree to be contacted about possible participation in future research.

Name of patient

Date

Signature

Name of researcher

Date

Signature

01/09/2011

University Hospital of North Staffordshire 
NHS Trust



K E E L E
U N I V E R S I T Y



K E E L E
UNIVERSITY

Keele Neuropsychology Parkinson's Research Group,
School of Psychology,
Keele University,
Keele,
Staffordshire ST5 5BG.

Healthy Volunteer CONSENT FORM

Title of Project: Dopaminergic medication and recognition memory in Parkinson's

Investigators: Dr Simon Ellis, Mr Thomas Shepherd, and Dr Nicky Edelstyn

Please initial box

- 1 I confirm that I have read and understand the information sheet dated September 1st, 2011 for the above study and have had the opportunity to ask questions.
- 2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3 I understand that data collected about me during this study will be anonymised before it is submitted for publication in scientific and medical journals and presented at conferences.
- 4 I agree to take part in this study.
- 5 I agree to be contacted about possible participation in future research projects.

Name of participant

Date

Signature

Name of researcher

Date

Signature

1 for participant, 1 for researcher.

Appendix D

Appendix E

APPENDIX
THE FOLSTEIN MINI-MENTAL STATE EXAMINATION

Name _____ Age _____ DOB _____ Place Seen _____ Date _____

Ask patient his:

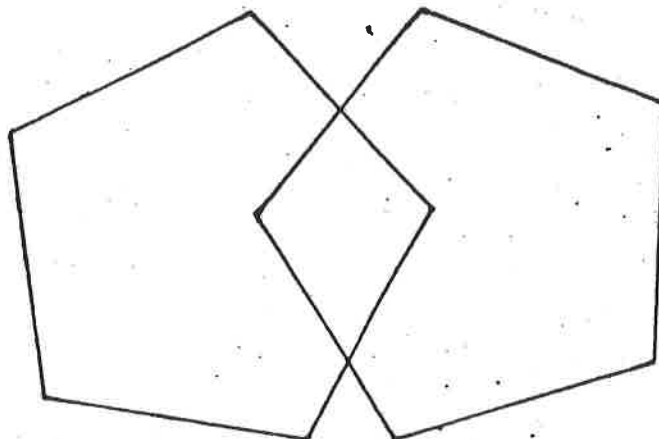
Name _____ Date of Birth _____ Occupation _____

- | | Maximum
Correct
Score | Patient's
Score
() | |
|----|-----------------------------|---------------------------|---|
| 1) | 5 | () | ORIENTATION
What is the - date _____, day of week _____, month _____
- season _____, year _____? |
| 2) | 5 | () | Where are we - name of province _____, town _____,
- street _____, place _____, floor _____? |
| 3) | 3 | () | REGISTRATION
Name 3 objects (HOUSE, TREE, CAR). Take 1 second to say each.
Then ask the patient all 3 after you have said them.
Give 1 point for each correct answer. Then repeat them until he learns all 3.
Count trials and record. TRIALS _____ |
| 4) | 5 | () | ATTENTION AND CALCULATION
Serial 7's. $100-7=()$ $93-()$ $86-()$ $79-()$ $72-()$ 65 .
One point for each correct answer. (Alternatively spell "WORLD" backwards). |
| 5) | 3 | () | RECALL
Ask for 3 objects - HOUSE (), TREE (), CAR (). |
| 6) | 9 | () | LANGUAGE
Name a pencil, and watch () 2 points
Repeat the following - "NO IFS, ANDS OR BUTS" _____ 1 point
Follow a 3-stage command:
"Take the paper in your right hand, fold it in half, and put it on the floor."
() 3 points
Read and obey the following: CLOSE YOUR EYES () 1 point
Write a sentence 1 point
Copy design 1 point (See diagram below) |

Alert Drowsy Stupor Coma

_____ = Total Score

Assess level of consciousness along a continuum



Appendix F

Hoehn and Yahr Staging of Parkinson's Disease.

Stage 0 – No signs of disease.

Stage 1 – Unilateral disease.

Stage 1.5 – Unilateral plus axial involvement.

Stage 2 – Bilateral disease, without impairment of balance.

Stage 2.5 – Mild bilateral disease with recovery on pull test.

Stage 3 – Mild to moderate bilateral disease; some postural instability; physically independent.

Stage 4 – Severe disability; still able to walk or stand unassisted.

Stage 5 – Wheelchair bound or bedridden unless aided.

Appendix G

338 Parkinson's disease and other movement disorders

Tremor

- 0 = Absent
- 1 = Slight and infrequently present
- 2 = Moderate; bothersome to patient
- 3 = Severe; interferes with many activities
- 4 = Marked; interferes with most activities

Sensory complaints related to Parkinsonism

- 0 = None
- 1 = Occasionally has numbness
- 2 = Frequently has numbness, tingling, or aching; not distressing
- 3 = Frequent painful sensations
- 4 = Excruciating pain

III Motor examination

Speech

- 0 = Normal
- 1 = Slight loss of expression, diction and/or volume
- 2 = Monotone, slurred but understandable; moderately impaired
- 3 = Marked impairment, difficult to understand
- 4 = Unintelligible

Facial expression

- 0 = Normal
- 1 = Minimal hypomimia; could be normal 'poker face'
- 2 = Slight but definitely abnormal diminution of facial expression
- 3 = Moderate hypomimia; lips parted some of the time
- 4 = Masked or fixed faces, with severe or complete loss of facial expression; lips parted $\frac{1}{4}$ inch (6 mm) or more

Tremor at rest

- 0 = Absent
- 1 = Slight, and infrequently present
- 2 = Mild in amplitude and persistent, or moderate in amplitude but only intermittently present
- 3 = Moderate in amplitude and present most of the time
- 4 = Marked in amplitude and present most of the time

Action or postural tremor of hands

- 0 = Absent
- 1 = Slight; present with action
- 2 = Moderate in amplitude; present with action
- 3 = Moderate in amplitude; present with posture-holding as well as with action
- 4 = Marked in amplitude; interferes with feeding

Rigidity

- Judged on passive movement with patient relaxed in sitting position; 'cogwheeling' to be ignored
- 0 = Absent
- 1 = Slight or detectable only when activated by mirror or other movements
- 2 = Mild to moderate
- 3 = Marked, but full range of motion easily achieved
- 4 = Severe, range of motion achieved with difficulty

Finger taps

- Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately
- 0 = Normal
- 1 = Mild slowing and/or reduction in amplitude
- 2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement
- 3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
- 4 = Can barely perform task

Hand movements

- Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.
- 0 = Normal
- 1 = Mild slowing and/or reduction in movement
- 2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement
- 3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
- 4 = Can barely perform task

Rapid alternating movements of hand

- Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.
- 0 = Normal
- 1 = Mild slowing and/or reduction in movement
- 2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement
- 3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
- 4 = Can barely perform task

340 Parkinson's disease and other movement disorders

Leg agility

Patient taps heel on ground in rapid succession, picking up entire leg; amplitude should be about 3 inches (7.5 mm).

0 = Normal

1 = Mild slowing and/or reduction in movement

2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement

3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement

4 = Can barely perform task

Arising from chair

Patient attempts to arise from a straight-backed wood or metal chair, with arms folded across chest.

0 = Normal

1 = Slow, or may need more than one attempt

2 = Pushes self up from arms of seat

3 = Tends to fall back and may have to try several times but can get up without help

4 = Unable to arise without help

Posture

0 = Normal erect

1 = Not quite erect, slightly stooped posture; could be normal for older person

2 = Moderately stooped posture; definitely abnormal; can be slightly leaning to one side

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side

4 = Marked flexion, with extreme abnormality of posture

Gait

0 = Normal

1 = Walks slowly, may shuffle with short steps but no festination or propulsion

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion

3 = Severe disturbance of gait; requires assistance

4 = Cannot walk at all even with assistance

Postural stability

Response to sudden posterior displacement produced by a pull on shoulders while patient is erect, with eyes open and feet slightly apart; patient is prepared.

0 = Normal

1 = Retropulsion but recovers unaided

2 = Absence of postural response; would fall if not caught by examiner

3 = Very unstable; tends to lose balance spontaneously

4 = Unable to stand without assistance

Body bradykinesia and hypokinesia
Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.

0 = None

1 = Minimal slowness giving movement a deliberate character; could be normal for some persons; possibly reduced amplitude

2 = Mild degree of slowness and poverty of movement that is definitely abnormal; alternatively some reduced amplitude of movement

3 = Moderate slowness; poverty or small amplitude of movement

4 = Marked slowness; poverty or small amplitude of movement

IV Complications of therapy (in the past week): dyskinesia

Duration
What proportion of the waking day are dyskinesias present? (Historical information)

0 = None

1 = 1-25% of day

2 = 26-50% of day

3 = 51-75% of day

4 = 76-100% of day

Disability

How disabling are the dyskinesias? (Historical information, may be modified by office examination)

0 = Not disabling

1 = Mildly disabling

2 = Moderately disabling

3 = Severely disabling

4 = Completely disabling

Painful dyskinesias

How painful are the dyskinesias?

0 = No painful dyskinesia

1 = Slightly

2 = Moderately

3 = Severely

4 = Markedly

Presence of early morning dystonia. (Historical information)

0 = No

1 = Yes

Complications of therapy (in the past week): clinical fluctuations

Are there any 'off' periods predictable as to timing after a dose of medication?

0 = No

1 = Yes

Appendix H

Epworth Sleepiness Scale

Name: _____

Date: _____

Your age: (Yr) _____ Your sex: ☐ Male ☐ Female

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

- 0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing
Sitting and reading	<input type="text"/>
Watching TV	<input type="text"/>
Sitting, inactive in a public place (e.g. a theatre or a meeting)	<input type="text"/>
As a passenger in a car for an hour without a break	<input type="text"/>
Lying down to rest in the afternoon when circumstances permit	<input type="text"/>
Sitting and talking to someone	<input type="text"/>
Sitting quietly after a lunch without alcohol	<input type="text"/>
In a car, while stopped for a few minutes in the traffic	<input type="text"/>
Total	<input type="text"/>

Appendix I

1. again
2. address
3. cough
4. preview
5. although
6. most
7. excitement
8. know
9. plumb
10. decorate
11. fierce
12. knead
13. aisle
14. vengeance
15. prestigious
16. wreath
17. gnat
18. amphitheatre
19. lieu
20. grotesque
21. iridescent
22. ballet
23. equestrian
24. porpoise
25. aesthetic
26. conscientious
27. homily
28. malady
29. subtle
30. fecund
31. palatable
32. menagerie
33. obfuscate
34. liaison
35. exigency
36. xenophobia
37. ogre
38. scurrilous
39. ethereal
40. paradigm
41. perspicuity
42. plethora
43. lugubrious
44. treatise
45. dilettante
46. vertiginous
47. ubiquitous
48. hyperbole
49. insouciant
50. hegemony



Appendix J

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name _____

Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)

- _____ **0=** Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT

- _____ **0=** Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

- _____ **0=** Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY

- _____ **0=** No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
2= Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE

- _____ **0=** No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE

_____ **0=** No difficulty

1= Waking in early hours of the morning but goes back to sleep

2= Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES

_____ **0=** No difficulty

1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies

2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)

3= Decrease in actual time spent in activities or decrease in productivity

4= Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____ **0=** Normal speech and thought

1= Slight retardation at interview

2= Obvious retardation at interview

3= Interview difficult

4= Complete stupor

9. AGITATION

_____ **0=** None

1= Fidgetiness

2= Playing with hands, hair, etc.

3= Moving about, can't sit still

4= Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)

_____ **0=** No difficulty

1= Subjective tension and irritability

2= Worrying about minor matters

3= Apprehensive attitude apparent in face or speech

4= Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____ **0=** Absent

1= Mild

2= Moderate

3= Severe

4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____ **0=** None

1= Loss of appetite but eating without encouragement from others. Food intake about normal

2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____ **0=** None

1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability

2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____ **0=** Absent

1= Mild

2= Severe

15. HYPOCHONDRIASIS

_____ **0=** Not present

1= Self-absorption (bodily)

2= Preoccupation with health

3= Frequent complaints, requests for help, etc.

4= Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:

0= No weight loss

1= Probably weight loss associated with present illness

2= Definite (according to patient) weight loss

3= Not assessed

17. INSIGHT

_____ **0=** Acknowledges being depressed and ill

1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.

2= Denies being ill at all

18. DIURNAL VARIATION

_____ **A.** Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none

0= No variation

1= Worse in A.M.

2= Worse in P.M.

_____ **B.** When present, mark the severity of the variation. Mark "None" if NO variation

0= None

1= Mild

2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality;
Nihilistic ideas)

- _____ **0=** Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

- _____ **0=** None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

- _____ **0=** Absent
1= Mild
2= Severe

Total Score _____

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Appendix K

Objectives

There were two aims to this pilot work;

- i) To produce 4 independent versions of a recognition memory test, matched for imageability, concreteness and frequency ratings.
- ii) To assess how closely the four versions of the recognition memory tests are matched for difficulty, to be used in future work with four experimental conditions.

Method

Design

To develop the 4 versions of the recognition memory test, 400 nouns were divided into 8 lists of 50 words. The 8 lists of 50 words with their individual and means and standard deviations for imageability, frequency and concreteness ratings (Franklin, Hoffman & Rubin, 1982) are presented in Tables K1, K2, K3, K4, K5, K6, K7 and K8.

Table K1.

Words included in List 1 and the imageability, frequency and concreteness rating.

List 1	Imageability	Frequency	Concreteness
ABSENCE	3	53	3.7
ANCHOR	6.5	15	6.3
BASKET	6	17	6.7
BASIS	1.9	184	3.3
CABLE	5	7	6.4
CAMPAIGN	4.2	81	4.6
DUTY	3.3	61	3.2
EAGLE	6.3	5	6.9
FARMER	6.2	23	6.6
GENIUS	4.9	23	3.8
GESTURE	5.1	32	4.5
HOTEL	6.5	126	6.8
ISLAND	6.6	167	6.6
JACKET	6.3	33	6.6
KITCHEN	6.3	90	6.8
SPIRIT	4	182	2.3
LEARNING	3.9	60	3.6
METHOD	2.3	142	4
NATION	4.2	139	4.9
NAVY	5.9	37	6.4
OBJECT	3.6	65	5.1
OCEAN	6.7	34	6.5
PAPER	6.1	157	6.9
COLUMN	4.9	71	5.6
RAILWAY	6.5	12	6.5
RATTLE	5.6	5	5.5
RIVER	6.6	165	6.6
ROBBER	5.8	2	6
SERIES	3.2	130	4
SERVANT	5.2	19	6
SHERIFF	6.3	20	6.8
TALENT	4.2	40	3.7
TEACHER	6.2	80	6.4
TEMPER	4.7	12	3.8
TRIUMPH	4.8	22	3.6
TROUBLE	3.5	164	3
TUNNEL	6.3	10	6.4
TWILIGHT	5.3	4	4.8
CAPTAIN	6	85	6.7
MAKER	2.8	12	3.9
MOTOR	5.8	56	6.5
PATIENCE	3.4	22	2.6
CUSTOM	2.7	14	3.2
DANGER	4.9	70	3.8
CREDIT	2.7	64	3.3
CORNER	5.8	115	6.1
SILENCE	4.6	52	3.5
SUCCESS	4.3	93	3.7
TRIBUTE	2.9	24	3.8
CHIMNEY	6.2	7	6.7
Mean	4.32	62.06	5.1
Standard deviation	1.37	55.09	1.47

Table K2.

Words included in List 2 and the imageability, frequency and concreteness rating.

List 2	Imageability	Frequency	Concreteness
ACCORD	1.8	9	2.6
BATTLE	6.1	87	5.3
ANGLE	4.7	51	4.9
APPLE	6.7	9	6.9
CAPTIVE	4.8	5	4.5
CARBON	4.5	30	5.9
CAREER	4.4	67	4.8
PARCEL	6.3	1	6.5
DETAIL	2.9	72	4.1
DEVICE	3.2	55	4.6
DEVIL	5.8	25	3.9
CIRCLE	6.1	60	6.4
CURRENT	3.1	104	3.8
EFFECT	2.4	213	3
FUTURE	3.5	227	3.5
JUDGMENT	3	60	2.9
LIQUOR	6.5	43	6.7
PISTOL	6.1	27	6.8
PITCHER	6.5	21	6.5
PLANET	6.1	21	6.1
POLICE	6.5	155	6.6
SAILOR	6.3	5	6.6
SALAD	6.3	9	6.5
SANDWICH	6.7	10	6.7
LETTER	6.2	145	6.2
TRAFFIC	6.1	68	5.8
VILLAGE	6.3	72	6.2
SUPPER	6.2	37	6.3
SURFACE	4.7	200	5.4
HIGHWAY	6.4	40	5.7
HORROR	5	17	3.3
HOTEL	6.5	126	6.8
ESTATE	5.8	51	6
INCOME	3.4	109	5.1
INSECT	6.3	14	6.7
MOISTURE	5.3	10	5.5
EXTENT	2	110	2.8
FABRIC	5.5	15	6.4
FACTOR	2.2	71	3.7
WILLOW	6.1	9	5.9
WINDOW	6.6	119	6.6
CANDLE	6.6	18	6.9
ILLNESS	4.5	20	5
IMAGE	3.9	119	3.7
TIMBER	5.8	19	6.5
TOTAL	3.7	211	4.4
SULPHUR	4.1	3	6.5
SUMMER	6.1	134	5.9
SICKNESS	4.7	6	4.7
MERIT	2.7	29	3.1
Mean	5.06	62.72	5.34
Standard deviation	1.48	61.48	1.32

Table K3.

Words included in List 3 and the imageability, frequency and concreteness rating.

List 3	Imageability	Frequency	Concreteness
ACCOUNT	2.6	117	4
ANGEL	5.9	18	4
BARREL	5.6	24	6.8
BUTTON	6.3	10	6.8
CABIN	6.5	23	6.5
DAUGHTER	5.7	72	6.5
DAYLIGHT	6.5	15	6.2
EFFORT	3.6	145	2.9
FEELING	3.8	172	2.1
FEVER	5	19	4.7
LEVEL	3.5	213	4
LILY	5.9	1	6.7
MACHINE	6	103	6.6
MAJOR	3.6	247	3.9
OYSTER	5.8	6	6.8
PACKAGE	5.8	20	6.5
QUARTER	5.6	34	5.9
SHELTER	5.8	70	5.9
SHEPHERD	5.8	3	6.5
TICKET	6	16	6.6
TIGER	6.6	7	7
WITNESS	4.4	28	5.1
WORKER	5.4	30	6.3
REFUGE	3.7	7	4.2
SINGER	4.2	10	3.3
SINGLE	6.4	172	6.5
SISTER	1.6	38	2.5
MUSIC	6.1	216	5.3
NATION	4.2	139	4.9
MOVIE	6.1	29	6.4
MUSCLE	6	42	6.5
HARNESS	5.5	10	6.2
HARVEST	5.7	12	5.8
BELIEF	2.6	64	2.5
BERRY	5.5	9	6.6
CHAPEL	5.9	20	6.7
CHAPTER	4.5	74	5.5
LION	6.7	17	7
LIQUID	5.4	48	6.1
COLOUR	5.2	141	5.5
CHAIRMAN	4.7	67	5.7
CATTLE	6.4	97	6.9
TRIUMPH	4.8	22	3.6
MARKET	5.6	155	6.1
CHIMNEY	6.2	7	6.7
MOMENT	2.2	246	3
MONARCH	5.1	3	5.9
COMPOUND	2.7	11	3.3
PUZZLE	5.5	10	5.5
WORSHIP	4.7	36	2.8
Mean	5.1	61.9	5.93
Standard deviation	1.26	69.77	1.46

Table K4.

Words included in List 4 and the imageability, frequency and concreteness rating.

List 4	Imageability	Frequency	Concreteness
ACID	4.4	13	6.1
ARTIST	6	57	5.4
ASPECT	1.7	47	2.5
ATTACK	5.4	105	4.6
FOREST	6.6	66	6.7
SPIDER	6.8	2	7
SQUIRREL	6.3	1	6.9
MESSAGE	4.7	64	4.8
METAL	5.6	61	6.6
DISTRICT	3.3	135	4.3
DOLLAR	6.6	46	6.6
CLUSTER	4.3	13	4.5
COFFEE	6.4	78	6.7
COUSIN	5.8	51	6.3
FINGER	6.3	40	6.9
FLAVOR	3.5	16	4.6
HATRED	4.5	20	3
HEAVEN	5	43	2.5
NOTHING	3.5	412	3
NOTION	2.1	40	2.4
LUMBER	6.1	35	6.8
WAGON	6.2	55	6.7
PENNY	6.5	25	6.8
PEPPER	6.3	13	6.8
PERFUME	6	10	6.3
HUSBAND	5.9	131	6.1
VALLEY	6.3	73	6.4
WIDOW	5.4	26	6.3
COUNTY	4	155	5.4
WEAPON	6	42	6.2
WEAKNESS	3.1	46	3.4
RESEARCH	4	171	4.7
RESORT	5.2	12	5.1
PASTURE	6.2	14	6
PATENT	2.3	35	4.7
COLLEGE	6	267	6.1
COMMERCE	2.8	58	4.1
LEADER	5.2	74	5.2
DIAMOND	6.6	8	6.6
SCHOLAR	5.5	15	6.3
BUSHEL	5.4	1	6.4
MATTER	2.7	308	3.9
MAYOR	5.4	38	6.6
MEADOW	6.1	17	5.9
STOMACH	5.8	37	6.6
LIMIT	2.5	48	2.7
LINEN	6.1	6	6.6
ORANGE	6.6	23	6.1
SOLDIER	4.4	39	4.6
PRAYER	4.5	28	5
Mean	5.08	62.4	5.44
Standard deviation	1.4	79.46	1.38

Table K5.

Words included in List 5 and the imageability, frequency and concreteness rating.

List 5	Imageability	Frequency	Concreteness
ACRE	4.6	9	5.7
AUTHOR	4.6	46	5.9
BABY	6.6	62	6.6
BANNER	5.8	8	5.8
CELLAR	5.7	26	6.5
CENTER	4.6	224	4.4
MOTHER	6.4	216	6.6
MOTION	4.4	55	4
EMPIRE	4.4	22	5
ENGINE	6.4	50	6.6
ERRAND	3.9	7	4.5
FATHER	2.4	183	3.2
FEATHER	6.2	6	6.5
GARDEN	6.5	60	6.5
JUSTICE	3.8	114	3.1
KEEPER	3.3	3	5.3
KINDNESS	4.4	5	3.1
MISTRESS	5.2	5	5.7
MIXTURE	3.7	30	4.2
NEEDLE	6.4	15	6.6
NEPHEW	5	9	6.4
ONION	6.5	15	6.7
OPERA	6.1	47	6
PARTNER	5.4	32	5.7
PARTY	6.4	216	5.7
PICTURE	6.2	162	6.5
RIDER	5.3	16	6.2
RIFLE	6	63	6.7
SECTION	2.8	189	4.6
SHERIFF	6.3	20	6.8
SHIPPING	3.8	19	4.5
LECTURE	6	16	5.5
LEGEND	3.8	26	3.9
TEMPLE	6	38	5.9
THEATER	6.4	52	6.5
UNCLE	5.9	57	6.3
UNION	3.5	182	4
PRESSURE	3.5	185	4.3
PRINCESS	6	10	6
RUBBER	5.8	15	6.4
RECEIPT	4.9	4	6
CONTEST	3.9	26	4.8
WRINKLE	6	2	5.2
CONTRACT	4.6	60	5
CORNER	5.8	115	6.1
MEMBER	3.1	137	5.2
MERCHANT	5.1	20	6.2
MERCY	3	20	3.1
WEDDING	6.5	32	5.8
REASON	2.5	241	2.3
Mean	5.03	63.44	5.40
Standard deviation	1.25	71.29	1.17

Table K6.

Words included in List 6 and the imageability, frequency and concreteness rating.

List 6	Imageability	Frequency	Concreteness
AFFAIR	5.3	33	3.7
AUTUMN	6.3	22	5.4
BEDROOM	6.4	52	6.7
BEGGAR	6.1	2	5.8
CANNON	6.5	7	6.4
CANOE	6.4	7	6.8
CANVAS	5.1	19	6.2
DEALER	4.2	25	5.7
DEGREE	3	125	3.4
DESPAIR	4.3	21	2.8
FEATURE	3.4	37	3.8
GARMENT	5.4	6	6.6
JOURNEY	4.9	28	5
ECHO	4.7	10	4.6
ELBOW	6	10	6.8
LADY	6.4	80	6
LANGUAGE	3.9	109	4.9
INTEREST	3.2	330	3.3
COUNTRY	5.8	324	5.1
MEANTIME	1.7	12	2.3
MEETING	4.6	159	5
DISTANCE	4.7	108	4.1
DOORWAY	5.8	15	6.7
EXCESS	3.6	42	3.2
FAILURE	2.7	89	3.1
MILLION	5.6	204	5
MINUTE	4.5	53	4.7
MIRROR	6.4	27	6.7
NAVY	5.9	37	6.4
OVEN	6	7	6.9
OWNER	4.4	33	6
PLAYER	5.3	51	5.8
PLEASURE	5	62	3.3
POCKET	6.2	46	6.5
PROJECT	3.6	93	4.9
SADDLE	6.1	25	6.5
SPEAKER	4.9	49	6.1
TREASURE	5.9	4	5.1
TROUBLE	3.5	164	3
TUNNEL	6.3	10	6.4
VELVET	6.2	4	6.3
KITTEN	6.4	5	7
SUBJECT	2.8	161	4.4
PARENT	6.3	15	6.2
PARLOR	5.5	18	6
STATION	5.7	105	6
UNIT	3	103	4.6
PAINTING	6.4	59	6
PALACE	6.3	38	6.2
PROVINCE	4.5	15	5.3
Mean	5.06	61.2	5.29
Standard deviation	1.25	73.39	1.29

Table K7.

Words included in List 7 and the imageability, frequency and concreteness rating.

List 7	Imageability	Frequency	Concreteness
AGENT	4.4	44	5.2
ARMOR	5.5	4	5.6
VIRTUE	3.1	30	2.1
BUBBLE	6.1	12	6.2
BUILDING	6.3	160	6.8
BULLET	6	28	6.9
CIRCUIT	3.8	23	4.7
CITY	6.4	393	6.3
CLIMATE	5.2	26	5
GODDESS	4.6	3	4
FRONTIER	5.2	30	4.9
FUNERAL	5.9	33	6.4
JOURNAL	4.8	42	6.4
EVENING	5.8	133	5.2
EVENT	3.3	81	4.7
DIET	3.7	21	4.6
DINNER	6.1	91	6.3
BUSINESS	4.4	392	5.1
BUTCHER	6	8	6.7
GOODBYE	4.8	6	3.6
HABIT	3.1	23	3.9
HAMMER	6.5	9	6.8
IRON	6.1	43	6.7
JERSEY	5	25	5.9
MONKEY	6.5	9	6.9
MONSTER	6	6	5.3
KINGDOM	4.8	26	4.8
LAUGHTER	6.1	22	5.4
LAWYER	5.9	43	6.7
MARRIAGE	5.6	95	4.2
ODOR	5.1	14	5
OFFENCE	3	8	3.9
PATIENT	4.3	86	4.9
PATTERN	4.8	86	5
RESOURCE	2.8	9	4.5
RIBBON	5.8	12	6.5
THEORY	2.5	129	3
THUNDER	5.8	14	5.6
STORY	5.1	153	5.4
SUGAR	6.4	34	6.7
WISDOM	4.2	44	3.2
WATER	6.5	442	6.6
SENTENCE	4.8	34	5.2
TURKEY	6.6	9	6.8
PUPIL	5.8	20	6.2
PURSUIT	4.1	16	3.4
INSTANT	3	38	3
MADAM	6.5	2	5.7
MOUNTAIN	6.6	33	6.7
COMPASS	5.8	13	6.6
Mean	5.13	61.2	5.29
Standard deviation	1.25	73.39	1.29

Table K8.

Words included in List 8 and the imageability, frequency and concreteness rating.

List 8	Imageability	Frequency	Concreteness
AMOUNT	2.8	172	3.8
BLESSING	3.2	10	3.1
BODY	6.4	276	6.2
BOTTOM	5.2	88	5.3
ARROW	6.4	14	6.8
COMRADE	4.2	4	5.2
CONCERT	5.9	39	6.3
CONGRESS	3.6	152	5
JEWEL	6	1	6.4
DOUBLE	4.6	5.6	4.7
DRAGON	6.2	1	5.9
FOOTBALL	6.7	36	6.9
FOREHEAD	6.3	16	6.9
ELDER	5.2	15	5.1
MEANING	2.1	127	2.8
PAYMENT	4.2	53	4.9
OLIVE	6.1	5	6.8
MASTER	4.1	72	5.2
RICHES	5.1	2	4.2
ARRAY	3	11	2.9
VESSEL	5.3	16	6.1
VICTIM	5.5	27	5.4
TRAINING	3.5	156	4.1
TRAITOR	4.2	2	4.8
MISSION	3.3	78	3.9
MISTAKE	3.4	34	4
DARKNESS	6.4	43	4.6
HELMET	5.9	1	6.8
PERSON	6.1	175	6.5
FORTUNE	3.9	25	3.5
FOUNTAIN	6.4	18	6.6
QUESTION	3.8	257	4.9
RABBIT	6.6	11	7
VAPOR	5	12	4.6
SCIENCE	4.1	131	3.8
SEASON	5.3	105	5.3
CARRIAGE	6.2	11	6.3
STATUS	3.1	97	3.1
ORGAN	5.9	12	6.6
OUTLINE	3.9	12	4.6
NOVEL	5.7	59	6
SYSTEM	2.8	416	4
PIGEON	6.4	3	6.9
PILLOW	6.5	8	6.6
PILOT	6.1	44	6.7
PRODUCT	3.7	87	5.5
MANNER	2.5	124	2.9
MARBLE	5.9	21	6.4
CHERRY	6.3	6	6.8
PRAYER	4.5	28	5
Mean	4.91	62.37	5.27
Standard deviation	1.33	83.67	1.28

To assess the comparability of the imageability, frequency and concreteness ratings across the 8 lists, a series of repeated measures ANOVA were conducted. No significant differences emerged in imageability ratings ($F(7,49) = .19, p = .99$), frequency ratings ($F(7,49) = .006, p = 1.0$) or concreteness ratings ($F(7,49) = .32, p = .95$). These results suggest that the 8 lists of 50 words are sufficiently match for imageability, frequency and concreteness. The next stage was to test the comparative difficulty of 4 versions of a recognition memory test whereby the 8 lists were randomly assigned to 1 of 4 versions of a recognition memory test as either a 'target' list or a 'distractor' list.

A repeated measures design was used where participants took part in four independent testing sessions, approximately one week apart. In each session participants were administered one of the four version of the recognition memory test. The order of the tests were counterbalanced across participants. Outcome measures of recognition memory, familiarity and recollection were the dependent variables, and test version (1 vs. 2 vs. 3 vs. 4) was the independent variable.

Participants

Participants were recruited from two main sources; a Research Participation Time (RPT) programme at the school of Psychology, Keele University and through personal contact. Fifteen participants (mean age = 30.20, SD = 12.47) took part in this pilot study (6 females; 9 males).

Procedure

The recognition memory task was composed of two phases, a study phase and a test phase. At study, 50 target items were individually presented to participants who were asked to read each word aloud – to aid concentration – and to try to commit each word to memory for a later recognition task. Each word was presented for 3000 milliseconds followed by a 1000 millisecond inter-stimulus-interval. After a 10 minute retention interval, the 50 target items were intermixed with 50 distractor items and presented to the participant at the same rate as items in the study phase. Participants were asked to respond "yes" when they recognised a target word and "no" if

they did not. A correctly identified target was labelled as a hit, whereas the incorrect endorsement of a distractor item was defined as a false alarm. Following each endorsement – irrespective of accuracy – participants made a subjective judgement about the basis of their recognition, either feelings of familiarity in the absence of recollection (e.g. a “know” response), or an explicit recollection of the item being previously presented (e.g. a “remember” response). There were no time constraints to this stage. Participants were instructed that a “remember” response could be given if the remembered: (i) where the word appeared during the study phase; (ii) the word or words that appeared just before or after the word during the study phase; (iii) personal memories, mental images, or other words – not part of the study phase – that came to mind when the word was originally presented during the study phase; (iv) thinking that the word was associated with another word presented during the study phase; (v) an emotional reaction that the word triggered when it was originally presented. “Know” responses were recorded when participants recognised a word from the study phase, but failed to remember any details associated with the word when it was presented during the study phase. Participants were familiarized with the procedure for the test phase prior to the commencement of the test and regular checks were made throughout the test phase to ensure participants maintained a full understanding of the criteria for making the “remember/know” judgement. The recognition memory test instructions given to participants, the procedure and the criteria for justifications of either a familiarity or recollection judgement are consistent with the recommendations of Migo, Mayes and Montaldi (2012).

Performance measures

To eliminate extreme scores, a correction was made to the raw recognition memory test data (corrected probability score = $[Y + 0.5]/[N + 1]$, where Y is the raw score and N is the total number of target or distractor items, Snodgrass & Corwin, 1988). This ensures that a measure of discrimination accuracy (d') can be calculated in the presence of extreme scores of 0 and 1.

Recollection and familiarity are assumed to be stochastically independent at retrieval in this study

although 'remember' and 'know' responses are designed to be mutually exclusive. Participants are instructed to give a 'know' response – in the absence of recollection – so 'know' (familiar) responses exclude 'remember' responses (recollection). If familiarity and recollection are indeed stochastically independent, the number of 'know' responses will provide an underestimation of familiarity because the same number of recollected items should be familiar. Consequently, Yonelinas and Jacoby's (1995) independence formula has been applied to the corrected scores (Familiarity = know/[1-remember]). Estimates of RM and familiarity accuracy have then been calculated using signal detection theory (d'), whereas estimates of recollection have been calculated as a threshold measure (pr) whereby the corrected false alarm rate has been subtracted from the corrected hit rate.

Data analysis

To assess the comparability of the 4 versions of the recognition memory test recognition memory (d'), familiarity (d') and recollection (pr) estimates were analysed separately using a series of repeated measures analyses of variance (ANOVA) to detect for any within participant variability on each of these performance estimates. Partial eta squared values are also presented to indicate the percentage of the variance within the data that is attributed to the different version of the recognition memory test. Following this analysis, to assess parallel reliability between the 4 versions, Cronbach's Alpha values were calculated for each performance measure, recognition memory (d'), familiarity (d') and recollection (pr).

Results

Version analysis

The raw hit and false means and standard deviations for recognition memory, *know* and *remember* responses for participants across the four versions of the recognition memory tests are

presented in Table K9. Estimates of recognition memory (d'), familiarity (d') and recollection (pr) are presented in Figure K1.

Table K9.

The means and standard deviations of the raw hit rates, false alarm rates and performance estimates for recognition memory (d'), familiarity (d') and recollection (pr).

	RM-Test 1 Mean (SD)	RM-Test 2 Mean (SD)	RM-Test 3 Mean (SD)	RM-Test 4 Mean (SD)
Recognition Memory				
Hits	42.07 (3.17)	41.00 (3.32)	42.13 (2.70)	41.80 (2.46)
False Alarms	3.80 (2.14)	3.20 (1.97)	3.73 (2.58)	4.13 (2.07)
d'	2.44 (0.29)	2.42 (0.31)	2.47 (0.31)	2.35 (0.31)
Familiarity				
Hits	9.60 (3.98)	9.13 (3.16)	9.93 (2.66)	9.60 (3.60)
False Alarms	2.60 (1.06)	2.20 (1.15)	3.27 (1.98)	2.73 (1.53)
d'	1.72 (0.28)	1.71 (0.31)	1.71 (0.43)	1.68 (0.38)
Recollection				
Hits	3.47 (4.55)	32.00 (3.59)	32.60 (3.16)	32.40 (2.90)
False Alarms	1.20 (1.26)	1.00 (1.36)	0.93 (0.88)	1.33 (.98)
pr	0.61 (0.09)	0.61 (0.07)	0.62 (0.07)	0.61 (0.05)

Notes and abbreviations. d' , signal detection measure of discrimination accuracy; pr , threshold measure. SD, Standard deviation.

Analysis of RM (d') data from the 4 versions of the recognition memory test suggest that there were no significant differences between the four versions ($F(3,42)$, = .79, p = .51). A partial eta squared value of .05 suggests that only 5% of the variance in the data is explained by the alternative versions of the test.

Analysis of the familiarity (d') estimates across the 4 versions of the recognition memory test revealed no significant differences ($F(3,42)$, = .11, p = .98). A partial eta squared value of .004

suggests that Only 0.4% of the variance in the familiarity data is accounted for by the different versions of the recognition memory test.

No significant differences were found in the recollection (*pr*) performance across the 4 versions of the recognition memory tests ($F(3,42) = .44, p = .73$). A partial eta squared value of 0.3 suggests that only 3% of variance in the data is attributed to the difference in versions of the test.

In summary this analysis suggests a comparable within-participant performance across the 4 versions of the recognition memory test on overall recognition memory, familiarity and recollection estimates.

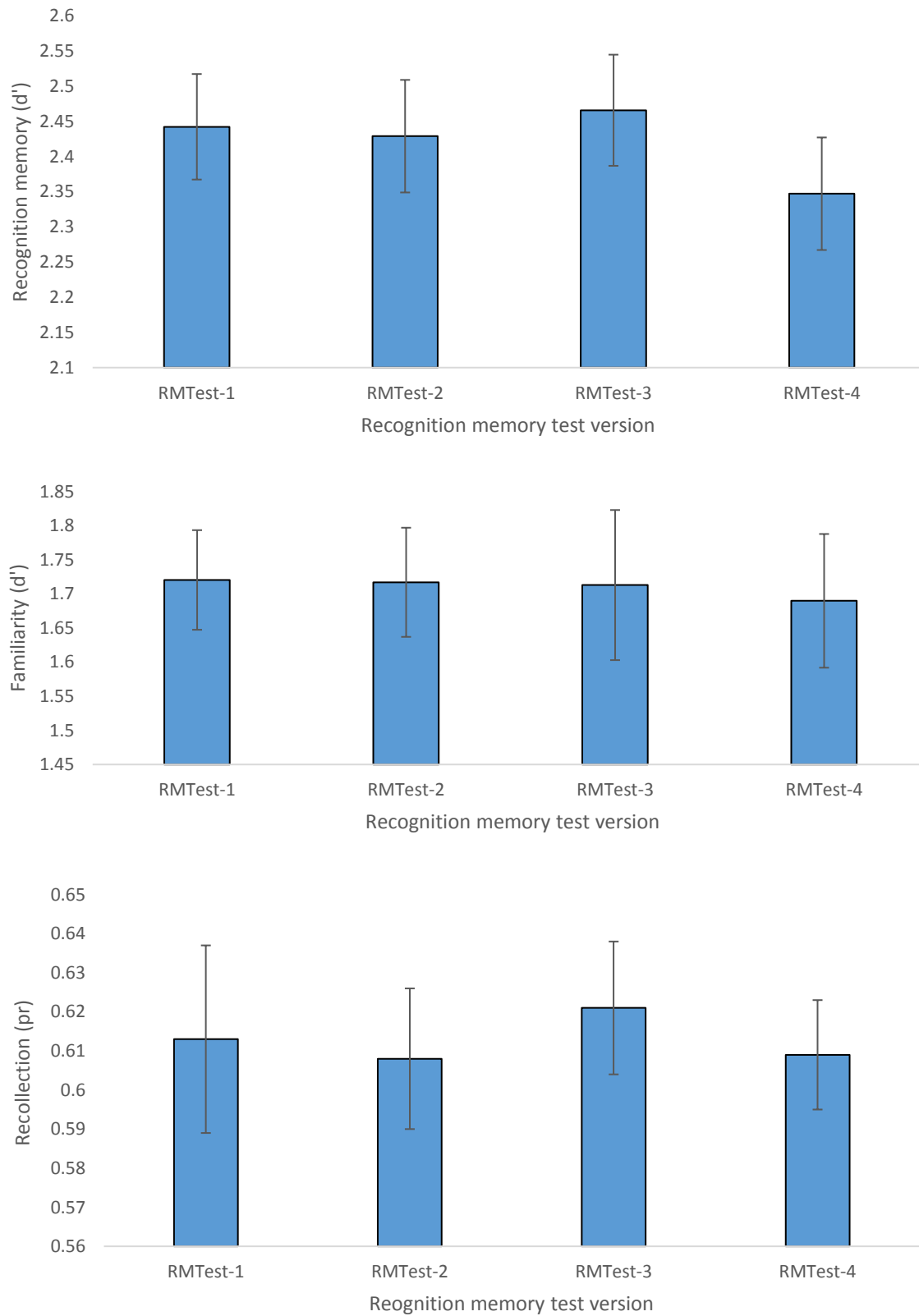


Figure K1. Means of recognition memory (d'), familiarity (d') and recollection (pr) estimates across the 4 versions of the recognition memory test. *Notes and abbreviations.* Error bars represent the standard error of the mean. RM, recognition memory.

Reliability analysis

To explore the parallel reliability or internal consistency of the 4 versions of the recognition memory test, Cronbach's alpha value were calculated. For overall recognition memory (d') across the 4 versions, $\alpha = 0.76$, familiarity, $\alpha = 0.86$, and recollection, $\alpha = .93$.

Discussion

There were two main aims to the piloting work. Firstly, to produce 4 versions of a recognition memory test consisting of 50 target words and 50 distractor words, where the words were matched for imageability, frequency and concreteness. The second aim was to test the comparative difficulty of the 4 versions of the recognition memory test in group of participants. The inferential statistical analysis, and effect sizes reported in the results section suggested that the 4 versions of the test were comparable on the three outcome measures assessed, recognition memory, familiarity and recollection. Cronbach's Alpha calculations also suggested a high degree of internal consistency and parallel reliability between the four versions ($\alpha > .75$) (DeVellis, 2003; Bland, & Altman, 1997; Nunnally & Bernstein, 1994).

In summary, the results of this piloting work suggests that the four versions of the recognition memory test are suitable for experiments with up to 4 testing conditions, to attribute any variation in performance across tests to other experimental manipulation.

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Appendix L

11. Digit Span (Optional)



DISCONTINUE RULE

After scores of 0 on both trials of any item. For both Digits Forward & Backward, administer both trials of each item even if trial 1 is passed.



RECORDING

All responses verbalized



SCORING RULE

0-1 pt. for each response

Digits Forward

Item/Trial	Response	Score 0 or 1
1. Trial 1 1 - 7		
Trial 2 6 - 3		
2. Trial 1 5 - 8 - 2		
Trial 2 6 - 9 - 4		
3. Trial 1 6 - 4 - 3 - 9		
Trial 2 7 - 2 - 8 - 6		
4. Trial 1 4 - 2 - 7 - 3 - 1		
Trial 2 7 - 5 - 8 - 3 - 6		
5. Trial 1 6 - 1 - 9 - 4 - 7 - 3		
Trial 2 3 - 9 - 2 - 4 - 8 - 7		
6. Trial 1 5 - 9 - 1 - 7 - 4 - 2 - 8		
Trial 2 4 - 1 - 7 - 9 - 3 - 8 - 6		
7. Trial 1 5 - 8 - 1 - 9 - 2 - 6 - 4 - 7		
Trial 2 3 - 8 - 2 - 9 - 5 - 1 - 7 - 4		
8. Trial 1 2 - 7 - 5 - 8 - 6 - 2 - 5 - 8 - 4		
Trial 2 7 - 1 - 3 - 9 - 4 - 2 - 5 - 6 - 8		

Forward Total Score
Range = 0 to 16

Digits Backward

Item/Trial	(Correct Response)/Response	Score 0 or 1
1. Trial 1 2 - 4 (4 - 2)		
Trial 2 5 - 7 (7 - 5)		
2. Trial 1 6 - 2 - 9 (9 - 2 - 6)		
Trial 2 4 - 1 - 5 (5 - 1 - 4)		
3. Trial 1 3 - 2 - 7 - 9 (9 - 7 - 2 - 3)		
Trial 2 4 - 9 - 6 - 8 (8 - 6 - 9 - 4)		
4. Trial 1 1 - 5 - 2 - 8 - 6 (6 - 8 - 2 - 5 - 1)		
Trial 2 6 - 1 - 8 - 4 - 3 (3 - 4 - 8 - 1 - 6)		
5. Trial 1 5 - 3 - 9 - 4 - 1 - 8 (8 - 1 - 4 - 9 - 3 - 5)		
Trial 2 7 - 2 - 4 - 8 - 5 - 6 (6 - 5 - 8 - 4 - 2 - 7)		
6. Trial 1 8 - 1 - 2 - 9 - 3 - 6 - 5 (5 - 6 - 3 - 9 - 2 - 1 - 8)		
Trial 2 4 - 7 - 3 - 9 - 1 - 2 - 8 (8 - 2 - 1 - 9 - 3 - 7 - 4)		
7. Trial 1 9 - 4 - 3 - 7 - 6 - 2 - 5 - 8 (8 - 5 - 2 - 6 - 7 - 3 - 4 - 9)		
Trial 2 7 - 2 - 8 - 1 - 9 - 6 - 5 - 3 (3 - 5 - 6 - 9 - 1 - 8 - 2 - 7)		

Backward Total Score
Range = 0 to 14

Total Score
Range = 0 to 30

(Sum Forward Total Score & Backward Total Score)

Appendix M

17. Do you need glasses for reading?

18. Are you colour-blind?

Total Score
Range = 0 to 14

2. Logical Memory I



RECORDING

Place a tick (✓) next to each story unit recalled verbatim. Write non-verbatim responses next to the story unit.



SCORING RULE

0-1 pt. for each story or thematic unit. See Administration and Scoring Manual (Chapter 4 and Appendix A) for scoring criteria.

Story A

Anna Thompson of South London, employed as a cook in a school canteen, reported at the police station that she had been held up on the High Street the night before and robbed of fifty-six pounds. She had four small children, the rent was due, and they had not eaten for two days. The police, touched by the woman's story, made up a collection for her.

(Turn page to record Story A Responses.)

2. Logical Memory I (continued)

	Score 0 or 1		
Story A	Story Unit	Thematic Unit	Scoring Criteria
Anna.			<i>Anna</i> or variant of the name
Thompson			<i>Thompson</i> is required
of South			<i>South</i> (in any context)
London,			<i>London</i> (in any context)
			indication of a main character who is female
employed			indication that she held a job
as a cook			<i>cook</i> or some form of the word is required
in a school			<i>school</i> is required
canteen,			<i>canteen</i> is required
			indication that main character is employed or is working
reported			indication that a formal statement was made to someone in authority (in any context)
at the police			<i>police</i> (in any context)
station			<i>station</i> (in any context) or a word or phrase denoting a police station
that she had been held up			indication that she had been held up (i.e., gunpoint or knife)
on the High Street			<i>the High Street</i> (in any context)
the night before			indication that the hold-up occurred the previous night
and robbed			indication that a robbery took place
of fifty-six pounds.			indication that an amount of money greater than £49 but less than £60 was taken from her
			indication that main character reported that she was robbed
She had four			<i>four</i> is required together with an indication that the children were hers
small children,			<i>children</i> or a synonym is required
			indication that main character had children
the rent was due,			a phrase indicating that the rent was due
and they had not eaten			indication that her children or the family were without food
for two days.			<i>two days</i> is required, or a phrase meaning about two days
			indication that characters were in need or required assistance
The police,			a word or phrase signifying one or more members of the police (in any context)
touched by the woman's story,			indication that her story evoked sympathy
			indication that the police felt sympathy for the woman
made up a collection			a phrase indicating that money was collected
for her.			indication that the money collected was for her or her children
			indication that the police directly responded to her need

Story A
Recall Unit Score
Range = 0 to 25

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Story A
Thematic Unit Score
Range = 0 to 7

Story B—1st Recall

2. Logical Memory I (continued)

At 6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. A weather report interrupted the programme to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old films.

Score 0 or 1		
Story B — 1st Recall	Story Unit	Thematic Unit
At 6:00		6:00 is required
on Monday		Monday is required
evening		evening (in any context)
Joe		Joe or variant of the name
Grant		Grant is required
of Liverpool		Liverpool is required
was watching television		indication that he was watching/listening to the television
as he dressed		indication that he was getting dressed
to go out.		indication that he was going out
A weather report		indication that there was an announcement about weather
interrupted the programme		indication of a break in the regularly scheduled programme
to warn that thunderstorms		indication that there was a warning about a storm
would move into the area		indication that the storm was coming
within the next 2 to 3 hours		a phrase meaning about 2 or 3 hours
and remain until morning.		indication that the storm would stay until morning
The announcer said		indication that someone was reporting about a storm
the storm could bring hail		indication that hail was possible
and up to 4 inches		4 inches is required
of rain		rain is required
and cause the temperature to drop		indication that the temperature would drop or decrease
by 15 degrees.		a relative decrease of 15 degrees is required
Joe decided to stay home.		indication that he decided to stay home
He took off his coat		indication that he took off outer clothing
and sat down		indication that he was sitting down
to watch old films.		indication of viewing films is required

Story B — 1st Recall
Unit Score
Range = 0 to 25

Story B — 1st Recall
Thematic Unit Score
Range = 0 to 8

1st Recall Total Score Calculation

+ =
 Story A Recall Unit Score Story B — 1st Recall Unit Score
 Range = 0 to 25 Range = 0 to 25

1st Recall
Total Score
Range = 0 to 50

Story B-2nd Recall

2. Logical Memory I (continued)

At 6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. A weather report interrupted the programme to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old films.

Score 0 or 1		
Story B — 2nd Recall	Story Unit	Thematic Unit
At 6:00		6.00 is required
on Monday		Monday is required
evening,		evening (in any context)
Joe		Joe or variant of the name
Grant	1	Grant is required
of Liverpool		Liverpool is required
was watching television		indication that he was watching/listening to the television
as he dressed		indication that he was getting dressed
to go out.		indication that he was going out
A weather report		indication that there was an announcement about weather
interrupted the programme		indication of a break in the regularly scheduled programme
to warn that thunderstorms		indication that there was a warning about a storm
would move into the area		indication that the storm was coming
within the next 2 to 3 hours		a phrase meaning about 2 or 3 hours
and remain until morning.		indication that the storm would stay until morning
The announcer said		indication that someone was reporting about a storm
the storm could bring hail		indication that hail was possible
and up to 4 inches		4 inches is required
of rain		rain is required
and cause the temperature to drop		indication that the temperature would drop or decrease
by 15 degrees.		a relative decrease of 15 degrees is required
Joe decided to stay home.		indication that he decided to stay home
He took off his coat		indication that he took off outer clothing
and sat down		indication that he was sitting down
to watch old films.		indication of viewing films is required
		indication that the character decided to watch old films

Story B—2nd Recall Unit Score
Range = 0 to 25

Story B— 2nd Recall Thematic Unit Score
Range = 0 to 8

Recall Total Score
Range = 0 to 75

Thematic Total Score
Range = 0 to 23

Learning Slope Calculation

- = Learning Slope
 Range = -25 to +25
 Story B—2nd Recall Unit Score Range = 0 to 25
 Story B—1st Recall Unit Score Range = 0 to 25

(Sum Recall Unit Scores for Story A, Story B-1st, Story B-2nd)

(Sum Thematic Unit Scores for Story A, Story B-1st, Story B-2nd)

12. Logical Memory II

Recall



ADMINISTER 25-35 MINUTES AFTER LOGICAL MEMORY I



RECORDING

Place a tick (✓) next to each story unit recalled verbatim. Write non-verbatim responses next to the story unit.



SCORING RULE

0-1 pt. for each story or thematic unit

Reminder Given? ☐ Yes ☐ No

Score 0 or 1		
Story A	Story Unit	Thematic Unit
Anna		Anna or variant of the name
Thompson		Thompson is required
of South		South (in any context)
London;		London (in any context)
		indication that main character is a female
employed		indication that she held a job
as a cook		cook or some form of the word is required
in a school		school is required
canteen,		canteen is required
		indication that main character is employed or is working
reported		indication that a formal statement was made to someone in authority (in any context)
at the police		police (in any context)
station		station (in any context) or a word or phrase denoting a police station
that she had been held up		indication that she had been held up (i.e., gunpoint or knife)
on the High Street		the High Street (in any context)
the night before		indication that the hold-up occurred the previous night
and robbed		indication that a robbery took place
of fifty-six pounds.		indication that an amount of money greater than \$49 but less than \$60 was taken from her
		indication that main character is female and she was robbed
She had four		four is required together with an indication that the children were hers
small children,		children or a synonym is required
		indication that main character had children
the rent was due,		a phrase indicating that the rent was due
and they had not eaten		indication that her children or the family were without food
for two days.		two days is required, or a phrase meaning about two days
		indication that the children were in need of a meal or food
The police,		a word or phrase signifying one or more members of the police (in any context)
touched by the woman's story,		indication that her story evoked sympathy
		indication that the police felt sympathy for the woman
made up a collection		a phrase indicating that money was collected
for her.		indication that the money collected was for her or her children
		indication that the police directly responded to her need

Story A Recall Unit Score
Range = 0 to 25

Story A Thematic Unit Score
Range = 0 to 7

12. Logical Memory II (continued)

Reminder Given? ☐ Yes ☐ No

Story B	Score 0 or 1		Scoring Criteria
	Story Unit	Thematic Unit	
At 6:00			6:00 is required
on Monday			Monday is required
evening,			evening (in any context)
Joe			Joe or variant of the name
Grant			Grant is required
of Liverpool			Liverpool is required
			indication that the character who is male
was watching television			indication that he was watching/listening to the television
as he dressed			indication that he was getting dressed
to go out.			indication that he was going out
			indication that the character was preparing to leave
A weather report			indication that there was an announcement about weather
interrupted the programme.			indication of a break in the regularly scheduled programme
			indication of a weather announcement
to warn that thunderstorms			indication that there was a warning about a storm
would move into the area.			indication that the storm was coming
			indication of a storm moving into the area
within the next 2 to 3 hours			a phrase meaning about 2 or 3 hours
and remain until morning.			indication that the storm would stay until morning
			indication of a storm duration
The announcer said			indication that someone was reporting about a storm
the storm could bring hail			indication that hail was possible
and up to 4 inches			4 inches is required
of rain			rain is required
and cause the temperature to drop			indication that the temperature would drop or decrease
by 15 degrees.			a relative decrease of 15 degrees is required
			indication of a storm's ability
Joe decided to stay home.			indication that he decided to stay home
			indication that the character decided to stay in
He took off his coat			indication that he took off outer clothing
and sat down			indication that he was sitting down
to watch old films.			indication of viewing films is required
			indication that the character decided to watch a film or TV

Story B Recall Unit Score
Range = 0 to 25

--	--

Story B Thematic Unit Score
Range = 0 to 8

Recall Total Score
Range = 0 to 50

--	--

Thematic Total Score
Range = 0 to 15

(Sum Recall Unit Scores for Story A & Story B)

(Sum Thematic Unit Scores for Story A & Story B)

12. Logical Memory II *(continued)*

Recognition



RECORDING
Circle Y or N



SCORING RULE
0-1 pt. for each item

Item	Circle Y or N	Score 0 or 1
Story A		
1. Was the woman's name Anna Thompson?	Y N	
2. Was the story setting in South London?	Y N	
3. Was the woman a cook?	Y N	
4. Did she work in a canteen?	Y N	
5. Did she have four children?	Y N	
6. Were the children teenagers?	Y N	
7. Did the robbery take place on the High Street?	Y N	
8. Did the woman report being robbed two nights before?	Y N	
9. Did she report the robbery at the Police Station?	Y N	
10. Was the woman robbed of 75 pounds?	Y N	
11. Did the family go without food for four days?	Y N	
12. Was the rent due?	Y N	
13. Did the police catch the thief?	Y N	
14. Did the police feel sorry for the woman?	Y N	
15. Did the police make up a collection?	Y N	
Story B		
16. Was the man's name Joe Green?	Y N	
17. Was it Sunday evening?	Y N	
18. Was it 6:00?	Y N	
19. Was the story setting in Liverpool?	Y N	
20. Was Joe dressing to go out?	Y N	
21. Was Joe watching television?	Y N	
22. Was the programme interrupted?	Y N	
23. Was the storm expected to move into the area on Tuesday?	Y N	
24. Was the storm expected to stay in the area through the night?	Y N	
25. Was the temperature predicted to drop 30 degrees?	Y N	
26. Did the announcer predict 10 inches of rain?	Y N	
27. Did the announcer warn of possible flooding?	Y N	
28. Did the announcer warn that it could hail?	Y N	
29. Did Joe decide to stay home?	Y N	
30. Did Joe sit down to watch a sports programme?	Y N	

Recognition Total Score
Range = 0 to 30

Percent Retention Calculation

$$\boxed{} \div \boxed{} \times 100 = \boxed{}$$

Percent Retention
Range = 0 to 100%

Logical Memory II
Recall Total Score
Range = 0 to 50

Logical Memory I
Story A Recall Unit
Score + Story B-2nd
Recall Unit Score
Range = 0 to 50

Appendix N

From: Bob Scott [mailto:Bob.Scott@nihr-ccf.org.uk]
Sent: 14 February 2012 08:15
To: Nicky Edelstyn
Subject: RE: PB-PG-0211-24101 - Edelstyn et al., Extension request

Dear Nicky

Sorry for the delay in getting back to you. I can confirm that the Committee are happy with your response. The next stage is that I am required to carry out a full budget scrutiny and will probably need to pass some queries back to you for clarification. I hope to complete this by later this week.

With kindest regards

Bob

Bob Scott
Programme Manager
Research for Patient Benefit Programme
Email: bob.scott@nihr-ccf.org.uk
Direct dial: 020 8843 8043
Programme Web: <http://www.ccf.nihr.ac.uk/RfPB>

Central Commissioning Facility
Grange House
15 Church Street
Twickenham TW1 3NL

Main reception: 020 8843 8057
Fax: 020 8843 8001
Web: www.ccf.nihr.ac.uk

Appendix O

Dr Darren Clement
UNIVERSITY HOSPITAL OF NORTH STAFFORDSHIRE NHS TRUST
R & D DEPARTMENT, WINDSOR HOUSE
223 PRINCES ROAD
STOKE-ON-TRENT
ST4 7JW
UNITED KINGDOM

20/11/2012

Dear Dr Darren Clement

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference: 13780/0001/001-0001
Eudract Number: 2012-000801-64
Product: Pramipexole dihydrochloride monohydrate extended release
Protocol number: BTG001

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 13/11/2012.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

**Clinical Trials Unit
MHRA**

Appendix P



Study title:	A Phase IV Acceptability and Feasibility Trial of the Effects of Medication on Memory in Idiopathic Parkinson's Disease without cognitive impairment
REC reference:	13/NW/0009
Protocol number:	BTG001 version 6.4
EudraCT number:	2012-000801-64
IRAS project ID:	106239

23rd June, 2014

Dear Kath,

I am notifying the Committee, on behalf of the sponsor, Dr Darren Clement, Research and Development Manager, University Hospital of North Staffordshire and Dr Simon Ellis, CI/PI, Consultant Neurologist, University Hospital of North Staffordshire, of the following substantial amendment for MeMory PaD.

REC approval is sought for minor amendments to the following existing documents:

1. The Case Report Form (abbreviated to CRF)

Minor changes have been made to the CRF version 1, which include:

- Blood test for renal and hepatic impairment - omitted in error from CRF v1 (page 2)
- Height will now be recorded to enable BMI to be calculated - omitted in error from

CRF v1 (page 3)

- Start date of first IMP - omitted in error from CRF v1 (page 5)
- Reminder for research nurse to call patient-participant 48 hours after starting IMP, plus filed for entering any adverse events - omitted in error from CRF v1 (page 6)

- Start date of second IMP - omitted in error from CRF v1 (page 8)

• Reminder for research nurse to call patient-participant 48 hours after starting second IMP, plus filed for entering any adverse events - omitted in error from CRF v1 (page 10).

Linked change made to flow diagram included in protocol (new version 6.5, date 23/06/2014) and in patient-participant information sheet (new version 3.2, date 23/06/2014)

2. The trial protocol (new version “6.5”, date 23rd June, 2014)

- The Keele University Sponsor Representative has been updated (Professor Ann Hughes has been replaced by Professor Brian Doherty).
- Lack of clarity regarding the consenting process: It is now stated that the CI/PI will take consent with the research nurse in attendance (see page 23, Section 4.5 Obtaining informed Consent, page 26-27).
- Liver and kidney function has to remain within a specified range for the 3 month duration of each patient-participant’s involvement in the study. Current practice is to do a blood test either at the screening visit (if a patient hasn’t had a blood test within the last 3 months) or at the mid-study visit (as the 3 month window covered by the pre-trial blood test has usually expired). To standardise practice for all patients entering the study, the protocol is to be changed so that baseline blood tests are performed at the screening visit (see Table 1, page 23; Step 3, pages 23-24).
- Linked changes have also been made to the patient-participant information sheet (new version 3.2, date 23/06/2014) and consent form (new version 4.1 23/06/2014)
- Previous practice was to provide patient-participants enrolled into the trial with 3 contact numbers: the Neurology Research Office (for general enquiries), the Neurology Ward (for emergencies) and the research nurse’s (Ms Hurlstone) personal mobile number. This latter option is no longer appropriate with changes in staffing, holidays and so on. In future, enrolled patient-participants will be provided with numbers for the Neurology Office and Neurology Ward.

3. End of study interview schedule

- A new question (Q13) has been included asking patient-participants for their opinion (liked/disliked) about each IMP.

REC approval is sought for following substantial amendment.

We have created the following new documents:

- Two versions of a new Trial Card has been developed (Drug Swap: from ropinirole to pramipexole, and from pramipexole to ropinirole). Experience gathered to date in the RCT has shown that patient-participants would benefit from an “aide memoire” helping them to remember the dose of the second IMP they switch to in the second phase of the RCT.

Accordingly, a new mid study visit trial card will be completed by the research nurse at the mid study visit (see page 37).

I hope the paperwork is in order and please don't hesitate to get back in touch if further clarification is required.

I look forward to hearing from you soon.

Best wishes,

A handwritten signature in black ink, appearing to read 'Nicky Edelstyn', with a long horizontal flourish extending to the right.

Nicky Edelstyn,

Professor of Cognitive Neuropsychology and Rehabilitation,

School of Psychology,

Keele University, Keele,

Staffordshire ST5 5BG.

Tel: 01782 734318

Email: n.edelstyn@keele.ac.uk

Appendix Q



MeMory-PaD feasibility study

University Hospital of North Staffordshire,
Neurology Research Unit,
First Floor Block B,
Stoke on Trent,
ST4 6QG.

Patient Information Sheet

03 October 2014

Title of Project: **Me**dication and **MeMory** in **Pa**rkinson's **D**isease: a Feasibility Study

Investigators: Dr Simon Ellis, Mr Tom Shepherd, Professor Nicky Edeltyn, Dr Keira Watts and Professor Julius Sim.

Invitation You are being invited to consider taking part in a research study investigating memory in Parkinson's Disease. This project is being jointly undertaken by Dr Simon Ellis, Consultant Neurologist with colleagues from Keele University. This study is part of Mr Tom Shepherd's PhD which is a much wider project looking at medication and memory in Parkinson's Disease and is funded by a National Institute of Health Research's *Research for Patient Benefit* award.

Before you decide, it is important for you to understand why this research is being done and what it will involve. Please take time to read this leaflet carefully and discuss it with your carers, friends and relatives if you wish. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part.

What is the study about? A lesser-known aspect of Parkinson's disease is memory impairment. Although worrying about memory loss may seem trivial in comparison to the marked movement abnormalities which characterise the condition, memory deficits can have far reaching consequences.

For example, difficulties recognising new acquaintances and remembering recent events can lead to self-consciousness, avoidance of social situations and consequently, social isolation and depression. The ability to relive past experiences is called “episodic memory” and it is this type of memory which is particularly affected by Parkinson’s disease in some patients

In a recent study in which you may have participated, there was a suggestion that some of the drugs used to control the motor symptoms of Parkinson’s disease *may* have side-effects on memory. Put another way, Parkinson’s disease itself may cause a decline in memory, and the severity of this decline *may be* increased by certain types of medication used to treat the motor symptoms.

This new study is a development of the previous study in two areas: firstly it will involve many more participants, and second, each participant will be assessed on their current medication and have an opportunity to try a different medication. Having many more participants and assessing their memory on different drugs we can find out if our earlier findings are generally representative of Parkinson’s disease.

Why have I been invited to take part? We are interested in the following two Parkinson’s disease drugs: slow-release preparations of pramipexole (also known as Mirapex) and ropinirole (also known as Requip). These drugs are used to control Parkinson’s disease either alone, or in combination with l-dopa (also known as sinemet or madopar) and or other Parkinsonian drugs.

Only participants currently taking slow-release preparations of pramipexole or ropinirole (with or without other Parkinson’s drugs) **are eligible to take part.**

However, this is not the only factor in determining eligibility to take part in the study. Other criteria include being aged between 50-80 and have mild or moderate Parkinson’s disease, and participants MUST NOT “tick” any of the following exclusion criteria:

- English is a second language.

MeMory-PaD feasibility study

- Cognitive impairment as assessed with the Mini-Mental State Examination scoring of 25 or less (assessed at the Screening visit)
- Familial Parkinson's disease;
- Severe Parkinson's disease, indicated by a score of 5 on the Hoehn and Yahr disease severity rating scale (assessed at the screening visit)
- Unable to provide informed consent due to cognitive decline (problems with thinking, determined at the screening visit)
- Diagnosed with another neurological illness (other than Parkinson's disease) such as Alzheimer's disease, Multiple Sclerosis
- History of learning difficulty including dyslexia;
- Physical inability to attend or comply with testing scheduling, such as upper limb amputations, severe degenerative arthritis;
- Current or planned participation in another drug trial;
- Undergoing treatment for cancer;
- Family history of an allergic reaction to ropinirole or pramipexole;
- Prior or current history (within the previous 5 years) of significant and/or uncontrolled:
 - drug abuse or alcoholism;
 - major psychotic phenomenology including hallucinations or lack of awareness of dyskinesias;
 - hypotension: severe dizziness or fainting on standing;
 - impulse control disorders or compulsive behaviours;
 - incapacitating dyskinesias on a stable dose of l-dopa.
- Participants taking any of the following drugs:
 - COMT inhibitors (entacapone/COMTAN or tocapon/TASMAR),
 - apomorphine,
 - amantadine (population pharmacokinetic analyses suggest that amantadine may slightly decrease the oral clearance of pramipexole),
 - anticholinergics,
 - dopamine antagonists (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide,
 - ciprofloxacin
 - immediate-release preparations of either pramipexole or ropinirole.
- Participants treated with deep brain stimulation.
- Severe liver impairment

- Kidney impairment
- Women of child bearing potential unless they are using a recognised effective form of contraception or are not sexually active, and have no intention of becoming sexually active during the course of the trial.

Do I have to take part? You are free to decide if you wish to take part or not. If you do decide to take part you will be asked to sign two consent forms, one is for you to keep and the other is for our records.

We would also like to contact you about possible participation in future research studies. If you do not wish to receive this information then please **do not** tick point 9 on the consent form.

You are free to withdraw from this study at any time and without giving reason. You can do this simply by leaving a message on an answer phone (Tel: **01782 675391**). This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future. However we would like to use any data we have collected from you up until this point. The data we collect will be anonymized and there is no way anyone will be able to link the data with you as individual. Issues around how we keep data about you confidential and anonymous are outlined further on in this leaflet.

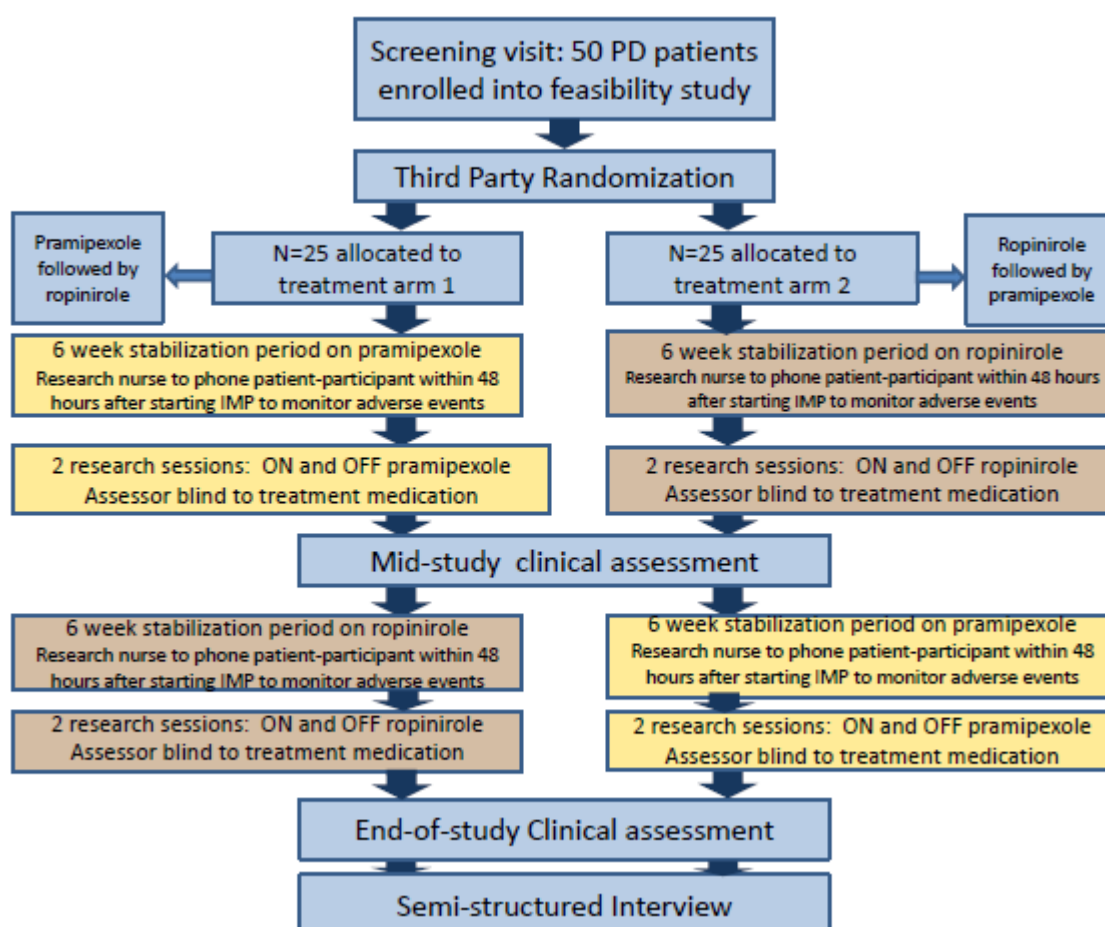
What will happen if I take part? Each participant will have 7 separate appointments, 4 of these will take place at your home and 3 will be in the hospital. The appointments are spread over a 16-18 week period. Travel expenses will be paid for the hospital visits which can be by car or taxi (please keep a receipt for your taxi-fare).

You will have the chance of trying a different medication which may suit your Parkinson's disease better and have no/fewer side-effects on memory. So participants on pramipexole will have the chance to try ropinirole instead, and those on ropinirole will try pramipexole.

MeMory-PaD feasibility study

Because participants will be changing their medication, it's important that their well-being is closely monitored as the new drug may have side-effects. So, we will arrange 3 visits: at the beginning of the study, a mid-study and end of the study, with Dr Simon Ellis and a research nurse where health and well-being will be monitored. There are also emergency phone numbers you can use if you need to urgently get in touch with Dr Ellis or one of the research nurses (provided at the end of the leaflet).

The design of the study is illustrated in the following flow chart, and is also described visit by visit on the next page. The research nurse will phone each patient-participant 48 hours after starting each IMP to monitor any adverse events



Screening visit (visit 1): This will take place in a clinic held in the Guy Hilton Research Centre. During this visit Dr Ellis will ensure you are eligible to take part, and carry out a physical examination. This visit will also provide you with an opportunity to find out more about the study, and have any queries addressed by Dr Ellis and a research nurse.

We will need to take a small blood sample (7.5 mls, just under 1 dessert spoon) to check your liver and kidney function is within the range required for inclusion in this trial. Further enrolment in the study will then have to stop until Dr Ellis gets the results back (which will probably take around a week). The research nurse will then phone you to either invite you back to continue enrolment into the trial. However, it may also be the case that liver and kidney function results fall outside the range specified for this trial, in which case the research nurse will explain this and what if anything needs to be done.

Of the participants enrolled into the study, half will first spend 6 to 7 weeks on ropinirole and then switch to pramipexole for another 6 to 7 weeks. The other half of our participants will have the sequence of drugs reversed. We have no control over which treatment arm participants will be allocated, this is done by a computer programme. It may be the case that participants already on pramipexole will be asked to switch to ropinirole for the first phase of the study and then revert back to pramipexole for the second phase. Alternatively they may remain on pramipexole for the first phase and then switch to ropinirole. The same scenarios apply to participants entering the study on ropinirole. Dr Ellis will discuss with them what to do for the first phase: i.e. stay on current medication or switch to the other drug. In cases where patient-participants do have to switch their drug, Dr Ellis will match the dose of the new drug to the old one and go through the possible side-effects of this new drug (side-effects of pramipexole and ropinirole are listed further on in this leaflet).

The research nurse will phone each patient-participant 48 hours after starting each trial medication (after the screening visit and then again after the mid study visit) to check how you're feeling and answer any queries you may have.

You will be given a 2 month supply of your FIRST trial medication at the screening session. All participants, irrespective of whether they are switching between ropinirole and pramipexole or remaining on the same drug, will obtain pramipexole / ropinirole from the hospital pharmacy for the duration of their involvement in the study. Participants are to take all other medication as normal – where or not they are related to Parkinson’s disease.

ON and OFF medication - home visits (visits 2 and 3): Participants are given 2 dates 6 weeks after starting the treatment, when they will have their memory assessed by Mr Tom Shepherd. These dates will be arranged with the research nurse at the screening visit and then again at the mid study visit. During this 6 week period which we call a “stabilisation period”, participants will take the trial medication (pramipexole or ropinirole) alongside their other medications. Both visits will take place on the morning (9:00 am), ideally within the same week, and take place in the participant’s home. The same assessments will be completed in both visits. The critical difference between these home-visits is that one will take place approximately 1 hour after the participant has taken their medication (we call this a medicated or ON session), whilst the other visit will take place following a period of medication withdrawal when the participant has not taken their pramipexole or ropinirole for a period of time (we call this an unmedicated or OFF sessions). The OFF session will allow us to establish the effects of Parkinson’s disease on memory, whereas the ON session will show us the additive effects of medication (plus Parkinson’s disease) on memory.

The research nurse will call you just before the withdrawal period to remind you how to prepare for the OFF research session, and talk you through any concerns you may have.

Preparation for the OFF research sessions differ for ropinirole and pramipexole because they are eliminated from the body at different rates. So for participants taking ropinirole, they will not take ropinirole on the day BEFORE the research session. Once the OFF research session is completed, they will resume their medication as normal. Dr Ellis will

explain fully how to prepare for the OFF session and what to do immediately it has been completed. For participants on pramipexole the washout period is longer. They need to stop taking this drug 2 DAYS before the research session. Again, Dr Ellis will go through with participants on pramipexole how to prepare for the OFF session and what to do after it.

The preparation for the OFF session may lead to participants motor symptoms becoming slightly worse for a short time. To help control the motor symptoms during this washout period, participants will be taking other Parkinson's disease drugs such as l-dopa and monoamine oxidase inhibitors. These are to be taken as normal up until the night before the OFF session and NOT taken on the morning of the OFF session. They can be taken as normal once the OFF research session has been completed.

The order of the ON and OFF research sessions will vary between participants, so for some patients, the first research session will be completed in an OFF state whilst for others it will be in an ON state.

It's very important that during the ON/OFF research sessions you don't mention to Tom Shepherd which treatment drug you are currently on.

Part of the design of this study is that he remains "blind" to your drugs, so that when he is administering the memory tests and analysing your data later he isn't influenced by this knowledge.

This all sounds very complicated, but there will be lots of opportunity to ask further questions about the design at the screening visit, and then subsequently by phoning and speaking to the research nurse.

A study card will be provide that will give the detailed information concerning the dates of the ON and OFF sessions and when to start the wash-out periods . It will also have contact numbers for non-urgent as well as emergency contacts.

Mid-study visit (visit 4): Participants then return to the outpatients department in the University Hospital of North Staffordshire for a mid-study visit with Dr Ellis and a

research nurse. This visit will involve the same health checks performed at screening, and provides an opportunity for participants to discuss with Dr Ellis how the first study drug (particularly for those who had to switch from their routine one) has suited them. If you haven't had your liver and kidney function assessed in the past 3 months, you will need to have some blood taken (7.5 mls, just under 1 dessert spoon) to check your liver and kidney function is within the range required for inclusion in this trial. If you do need to have these checks done, then we will have to delay giving you the next trial medication until we get the results back (which will probably take around a week). The research nurse will then phone you to either invite you back to continue the mid-study visit. However, it may also be the case that liver and kidney function results fall outside the range specified for this trial, in which case the research nurse will explain this and what if anything needs to be done.

This visit also heralds the second phase of the study when participants switch to the other drug, so participants who were on ropinirole will now be given a 7 week prescription for pramipexole, and those who had been on pramipexole will be given a prescription for ropinirole. Participants will collect these drugs from the hospital pharmacy as before. Dr Ellis will go through with each participant how to take the drug and how to prepare for the OFF research session. The dates for the ON and OFF research sessions (both home-visits again with Mr Tom Shepherd) will be arranged and study cards issued. These will take place following a 6 week stabilisation period on the prescription drug.

ON and OFF medication - home visits (visits 5 and 6): Both visits which will again be in the morning (9:00am) will follow exactly the same format as visits 2 and 3, although the order of these visits (ON, OFF) may be reversed (but not necessarily so). Once completed, - participants will return to the outpatients department (UHNS) for an end of study visit with Dr Ellis and a research nurse.

End of -study visit (visit 7): This visit will involve the same health checks performed at screening and mid-study visits, and provides an opportunity for participants to discuss with Dr Ellis how the second study drug (particularly for those who had to switch from their routine one) has suited them. Dr Ellis will then recommend to the participant and GP whether or not to revert to their original medication or switch to the alternate medication.

Once they have completed their visit with Dr Ellis, participants and their carers will also be invited to meet with Tom Shepherd to discuss their experience of taking part in the study. This discussion will take the form of a short interview which, if consent is given, will be audio taped for later transcription. Participants will also be asked if they will allow anonymised direct quotes to be used in future work in relation to this project. The interview will focus on the participant's experience of taking part in research in general, and in this study particularly. What were the difficulties of taking part were and how these could be alleviated in future projects.

Unused trial medication It is VERY IMPORTANT that you return all unused TRIAL medication to the research team. This means that any trial medication dispensed at the first SCREENING VISIT is returned at the MID-STUDY VISIT, and any unused trial medication dispensed at the MID-STUDY VISIT is returned at the END OF STUDY VISIT.

Reported side-effects of the trial medications Both of the trial medications can cause side-effects. **If you experience any of the following side-effects, or are worried about the side-effects, you MUST use one of the contact numbers on your TRIAL CARD.**

Side effects reported for **Pramipexole modified release (Mirapexin® Prolonged Release)** from drug trials include:

- Very Common side effects (may affect 10% or more):

- Dizziness, abnormal, uncontrolled movements of the limbs (dyskinesia), sleepiness (somnolence)
- Nausea (feeling sick)
- Common side effects (may affect 1% to less than 10 %) include:
 - Abnormal dreams, urge to behave in an unusual way (behavioural symptoms of impulse control disorder (for more information see below)) and compulsions, confusion, hallucination, sleeplessness (insomnia).
 - Headache
 - Visual impairment including double vision, blurred vision and reduced clearness of vision (visual acuity).
 - Low blood pressure
 - Constipation, and vomiting
 - Fatigue (tiredness)
 - Swelling or fluid retention of the lower legs ankles feet or hands (peripheral oedema)
 - weight loss including decreased appetite.
- Uncommon side effects (may affect 0.1% to less than 1%) include:
 - Pneumonia
 - Increase in body fluid (due to inappropriate excess production of the hormone called antidiuretic hormone) *
 - Impulse control disorder (including binge eating*, compulsive shopping, hypersexuality, pathological gambling), libido disorder, excessive hunger / increased appetite (hyperphagia*), restlessness, out of touch with reality, decreased awareness, confusion (paranoia, delusion, delirium)

- Memory disturbance (amnesia), increased movements and inability to keep still (hyperkinesia), excessive daytime sleepiness, suddenly falling asleep, fainting (syncope)
 - Cardiac failure*
 - Difficulties to breathe (dyspnoea), hiccups
 - Skin rash, itching (pruritus) or hypersensitivity
 - Weight increase
- Rare side effects (may affect 0.01% to less than 0.1%) include:
 - Agitation, feeling elated or over excited (mania)

*These side effects have been observed in post-marketing experience and therefore the frequency is not greater than uncommon but might be lower.

Side effects reported for **Ropinirole modified release (Requip® XL) and Ropinirole Immediate Release from drug trials and/or post-marketed use** in patients taking adjuvant therapy with levodopa include:

- Very Common side effects (may affect more than 10% of people);
 - abnormal, uncontrolled movements of the limbs (dyskinesia)
- Common side effects (may affect more than 1% to less than 10 %) include:
 - Hallucinations
 - Sleepiness (somnolence)
 - Dizziness including vertigo
 - Low blood pressure
 - Low blood pressure upon sitting and standing
 - Nausea

- Constipation
- Swelling or fluid retention of the lower legs ankles feet or hands (peripheral oedema)
- Confusion
- Heartburn
- Uncommon side effects (may affect more than 0.1% to less than 1 %) include
 - Psychotic reactions including feeling out of touch with reality, decreased awareness, confusion (paranoia, delusion, delirium)
 - Sudden onset of sleep and excessive daytime sleepiness (somnolence)

Side effects reported for **Ropinirole modified release (Requip® XL) and ropinirole immediate release ropinirole from drug trials and/or post marketed use** in patients taking ropinirole monotherapy (ropinirole only) include:

- Very Common side effects (may affect more than 10% of people);
 - Sleepiness (somnolence)
 - Nausea
 - Fainting (syncope)
- Common side effects (may affect more than 1% to less than 10 %) include:
 - Hallucinations
 - Dizziness including vertigo
 - Constipation
 - Swelling or fluid retention of the lower legs ankles feet or hands (peripheral oedema)
 - Swelling or fluid retention of the leg (leg odema)
 - Vomiting

- Heartburn
- Stomach (abdominal) pain
- Uncommon side effects (may affect more than 0.1% but less than 1%) include
 - Low blood pressure and low blood pressure upon standing
 - Psychotic reactions including feeling out of touch with reality, decreased awareness, confusion (paranoia, delusion, delirium)
 - Sudden onset of sleep and excessive daytime sleepiness (somnolence)

The following events have been reported with ropinirole immediate release at unknown frequencies:

- Hypersensitivity reactions including raised, itchy skin (urticaria), skin swelling (angioedema), rash , itchy skin (pruritus)
- Aggression (Aggression has been associated with psychotic reactions as well as compulsive symptoms)
- Liver reactions mainly changes in liver tests (increased liver enzymes)
- Impulse control disorders (as described for Pramipexole) can also occur in patients taking ropinirole.

Please note although you will already be taking one of these drugs for your Parkinson's Disease, it is possible you may re-experience some side effects when you revert back to your original medication following the switch.

What do I have to do? If you wish to find out more about the study please return the response slip (attached to the covering letter) in the stamped addressed envelope. We will



MeMory-PaD feasibility study

send you a reminder letter just in case you're interested but have lost the response slip. We won't send anymore reminders.

If you don't want to take part in this study, you can either return the response slip telling us so or do nothing. However, we will be sending out reminder letters to everyone we haven't heard from.

What are the benefits of taking part? It is possible that the new medication may suit you better than the one you are currently on, however this is not guaranteed. The opposite is also true – the new agonist may cause more side-effects than your current one. However, in the long-term, this study will provide a greater understanding of the effects of different types of medication on memory in Parkinson's disease. This information will influence decisions that doctors make about medication management for patients with Parkinson's disease.

What if something goes wrong? We don't expect any problems to arise in this study. If you are harmed by agreeing to take part in this research, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of the study, you may address this to Professor Michael Murray at School of Psychology, Keele University, ST5 5BG or 01782 733311, alternatively you can phone the Patient Advice and Liaison Service (PALS) at the University Hospital of North Staffordshire on 01782 676450 or 676455. .

Will my taking part be kept confidential? All of the research data that we collect during the study will be kept strictly confidential. Any information which has your name, address and any other identifying information will be kept in a locked filing cabinet in the School of



MeMory-PaD feasibility study

Psychology. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name.

Who is organizing the research? Dr Simon Ellis, Consultant Neurologist, University Hospital of North Staffordshire; Mr Tom Shepherd, PhD student, School of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University; Dr Keira Watts, Research and Development Facilitator, Research and Development Department, University Hospital of North Staffordshire and Professor Julius Sim, Statistician, Keele University have organised the study.

Contact for further information Please contact the Neurology Research Nurses for further information if required, on 01782 675393.

Appendix R



University Hospital of North Staffordshire



National Institute for
Health Research

**MeMory-PaD
feasibility study**

Trial Drug Instruction Card

During this stage of the study, we will be asking you to swap your current medication as detailed below

Name:

Subject ID:

MEDICATION TO BE STOPPED
DATE _____

PRAMIPEXOLE M/R (*insert dose*) mg
Once a day

MEDICATION TO BE STARTED
DATE _____

ROPINIROLE M/R (*insert dose*) mg
Once a day

Please only use trial medication given – do not use own supply

Please continue as above until you are seen by the research team at your mid / end (delete as appropriate) study visit on _____

Please continue to take all other medication as usual. If you have any problems please contact the Neurology research nurses on 01782 675393 (non-urgent) or UHNS Neurology Ward 01782 676231 (Emergency contact).

***Please do not show this card to the PhD
Student***

Many Thanks

MeMory PaD Research Team



University Hospital of North Staffordshire



National Institute for
Health Research

**MeMory-PaD
feasibility study**

Trial Drug Instruction Card

During this stage of the study, we will be asking you to swap your current medication as detailed below

Name:

Subject ID:

MEDICATION TO BE STOPPED
DATE _____

ROPINIROLE M/R (*insert dose*) mg
Once a day

MEDICATION TO BE STARTED
DATE _____

PRAMIPEXOLE M/R (*insert dose*) mg
Once a day

Please only use trial medication given – do not use own supply

Please continue as above until you are seen by the research team at your mid / end (delete as appropriate) study visit on _____

Please continue to take all other medication as usual. If you have any problems please contact the Neurology research nurses on 01782 675393 (non-urgent) or UHNS Neurology Ward 01782 676231 (Emergency contact).

***Please do not show this card to the PhD
Student***

Many Thanks

MeMory PaD Research Team

Appendix S

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

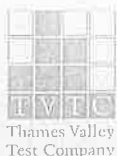
Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

Appendix T



the Hayling and Brixton tests

Scoring sheet

Subject and test details

Name

Age

Date of test

Further details

The Hayling Sentence Completion Test

Score summary

Box A

Box B

Box C

Total scaled scores

+ + =

(Section 1 Scaled score) (Section 2 Scaled score) (Section 2 Errors scaled score)

Hayling Section 1: sensible completion

- In a moment I am going to read you a series of sentences, each of which has the last word missing from it. I want you to listen carefully to each sentence, and when I have finished each one, your job is to give me a word which completes the sentence. Do you understand?

Practice

- Before we start, I'll give you a couple of practice sentences so that you can get the hang of it. Are you ready?

P1 The rich child attended a private

P2 The crime rate has gone up this

Test

- OK, that's the end of the practice items. The next few sentences I'll read aren't really any more difficult than the two you've just done. But the important thing is that I want you to give me your answer as quickly as you can—the faster the better. Is that clear?

1 He posted a letter without a
or: He mailed a letter without a

2 In the first space enter your
or: In the first blank enter your

3 The old house will be torn

4 It's hard to admit when one is

5 The job was easy most of the

6 When you go to bed turn off the

7 The game was stopped when it started to

8 He scraped the cold food from his

9 The dispute was settled by a third

10 Three people were killed in a major motorway
or: Three people were killed in an interstate

11 The baby cried and upset her

12 George could not believe that his son had stolen a

13 He crept into the room without a

14 Billy hit his sister on the

15 Too many men are out of

Response

Time

Total time (raw score)

Scaled score (transfer this to box A in score summary above)

Table E

Total scaled scores	Overall scaled score	Classification
23	10	Very superior
22	9	Superior
21	8	Good
20	7	High average
17-19	6	Average
15-16	5	Moderate ave.
13-14	4	Low average
11-12	3	Poor
10	2	Abnormal
<10	1	Impaired

Hayling overall scaled score

Table A

Raw score	Scaled score	Comment
0	7	High ave.
1-9	6	Average
10-18	5	Moderate ave.
19-22	4	Low ave.
23-50	3	Poor
51-60	2	Abnormal
>60	1	Impaired

Hayling Section 2: unconnected completion

- Now we are going to move on to the second section of the test. In this section I will read you a set of sentences with the last word missing just like the ones you have already done, but this time I want you to give me a word which does not fit at the end of the sentence – I want the word you give me to be completely unconnected to the sentence in every way. Do you understand?

Practice

- Before we start, I'll give you a couple of practice sentences so that you can get the hang of what is required! **Response**

	Response	Time
P1 London is a very busy		
P2 Her new shoes were the wrong		

- If the subject makes an error refer to instructions in Manual (page 8):

Test

- 'OK, that's the end of the practice items. Remember that the words you give me must be unconnected to the sentence, and that it is important for you to give me your answer as quickly as you can. Are you ready?'

[illegible]

Total time (raw score)

Scaled score (transfer this to box B in score summary on page 1)

Raw score	Scaled score	Comment
0	8	Good
1-2	7	High average
3-50	6	Average
51-60	5	Moderate ave.
61-100	4	Low average
101-120	3	Poor
121-130	2	Abnormal
> 130	1	Impaired

Converted score	Scaled score	Comment
0	8	Good
1-3	7	High average
4-9	6	Average
10-12	5	Moderate ave.
13-14	4	Low average
15-17	3	Poor
18-29	2	Abnormal
≥ 30	1	Impaired

Hayling 2 errors
scaled score
(transfer this to box
C in score summary
on page 1)

Appendix U

Appendix V

Starkstein's apathy scale

1. Are you interested in learning new things?	Not at all	slightly	some	a lot
2. Does anything interest you?	Not at all	slightly	some	a lot
3. Are you concern about your condition?	Not at all	slightly	some	a lot
4. Do you put much effort into things?	Not at all	slightly	some	a lot
5. Are you always looking for something to do?	Not at all	slightly	some	a lot
6. Do you have plans and goals for the future?	Not at all	slightly	some	a lot
7. Do you have motivation?	Not at all	slightly	some	a lot
8. Do you have the energy for daily activities?	Not at all	slightly	some	a lot
9. Does someone have to tell you what to do each day?	Not at all	slightly	some	a lot
10. Are you indifferent to things?	Not at all	slightly	some	a lot
11. Are you unconcerned with many things?	Not at all	slightly	some	a lot
12. Do you need to be pushed to get started on things?	Not at all	slightly	some	a lot
13. Are you neither happy nor sad, just in between?	Not at all	slightly	some	a lot
14. Do you consider yourself apathetic?	Not at all	slightly	some	a lot

For questions 1-8, not at all = 3, slightly = 2, some = 1, a lot = 0

For question 9-14, not at all = 0 slightly = 1 some = 2, a lot = 3

Appendix W

MeMory-PaD feasibility study

Neurology Research Unit, First Floor B Block
Newcastle Road, Stoke-on-Trent ST4 6QG

CONSENT FORM

Title of Project: Medication and meMory in Parkinson's Disease.

Investigators: Dr Simon Ellis, Mr Tom Shepherd, Professor Nicky Edelstyn, Dr Keira Watts and Professor Julius Sim

Please initial the box

- | | | |
|---|--|--------------------------|
| 1 | I confirm that I have read and understand the information sheet (version 3.4) dated 07 November 2014 for the above study and have had the opportunity to ask questions and have had these answered satisfactorily. | <input type="checkbox"/> |
| 2 | I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. | <input type="checkbox"/> |
| 3 | I understand that data collected about me during this study will be anonymised before it is submitted for publication in scientific and medical journals, and presented at conferences. | <input type="checkbox"/> |
| 4 | I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by authorized individuals (from Keele University, from regulatory authorities or from the NHS Trust) where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. | <input type="checkbox"/> |
| 5 | I agree to giving up to 7.5 mls of blood for the purpose of assessing liver and kidney function. | <input type="checkbox"/> |
| 6 | I agree to take part in this study. | <input type="checkbox"/> |
| 7 | I agree to my GP being informed about my participation in this study. | <input type="checkbox"/> |
| 8 | If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analyses. | <input type="checkbox"/> |



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University

**MeMory-PaD
feasibility study**

- 9 I agree to be contacted about possible participation in future research projects.
- 10 I agree to take part in an audio taped interview.
- 11 I agree that anonymised direct quotes from my interview may be used in any future work related to this project.

☐☐☐

Name of patient participant

Date

Signature

Name of researcher

Date

Signature

1 for patient participant, 1 for hospital record, 1 for site file.

Appendix X

MeMory-PaD

University Hospital of North Staffordshire,
Neurology Research Unit,
First Floor, Block B,
Stoke on Trent,
ST4 6QG.
Tel: 01782 675391.

3rd December 2013

Patient Information Sheet

Title of Study: Medication MeMory in Parkinson's Disease: a Feasibility Study.

Investigators: Dr Simon Ellis, Ms Sharon Hurlstone, Mr Tom Shepherd, Professor Nicky Edelstyn, Dr Keira Watts, Professor Julius Sim.

Invitation

You are being invited to take part in a research study investigating the concerns people have about taking part in research studies and the reasons they have decline to participate. The study is being carried out by Dr Simon Ellis, Consultant Neurologist, University Hospital of North Staffordshire, Ms Sharon Hurlstone, Research Nurse, Department of Neurology, University Hospital of North Staffordshire with colleagues from Keele University, Mr Tom Shepherd and Professor Nicola Edelstyn. The study is part of Mr Tom Shepherd's PhD, which is a much wider project looking at how medication affects memory in Parkinson's Disease and is funded by the National Institute of Health Research's *Research for Patient Benefit* grant.

Before you decide whether to take part or not, it is important for you to understand why this research is being done and what it will involve. You may also wish to discuss the study with family members before deciding. If anything is unclear or you would like more information our contact details are at the end of this leaflet, please don't hesitate to contact us.

MeMory-PaD

What is the study about?

There are many concerns that people with Parkinson's may have about taking part in research. This study aims to explore those concerns. We aim to do this by interviewing people with Parkinson's who recently declined to take part in a clinical trial investigating how Parkinson's medication affects their memory. It is important that we find out what people's main concerns are so that they can be addressed when designing research in the future.

Why have I been invited to take part?

You have been invited to take part because you recently declined to take part in a clinical trial investigating the effect of two Parkinson's drugs on memory. What we want to do is explore the concerns that lead to your decision so that in the future we can design research that is more appealing, more accessible and/or more relevant to you.

Do I have to take part?

You are completely free to decide if you wish to take part or not. Please feel free to discuss any aspect of the research with us (contact details are at the end of this leaflet).

If you do decide to take part you will be asked to sign two forms, one which provides your consent to take part and the second to say you are happy for us to use anonymised direct quotes from your responses. Even after you have provided consent you have the right to withdraw at any point, without giving a reason. Whether you decide to take part or not will NOT affect your current or future healthcare.

MeMory-PaD

What will happen if I take part?

If you wish to take part, you will be asked to take part in an interview at a time, date and location most convenient to you. The purpose of the interview will be to explore the concerns you had about the clinical trial you were recently invited to take part in. The interview will last approximately 30 minutes and will be recorded via an audio recorder, and transcribed at a later date. You may ask for the interview not to be recorded, or for the recorder to be turned off at any time without giving a reason. You may refuse to answer any question you do not want to answer during the interview.

What are the benefits of taking part?

There are no immediate benefits to you for taking part, however by highlighting the concerns you had about the research you were recently invited to take part in, we may be able to design studies that are more attractive or relevant to you in the future.

What if something goes wrong?

There are no anticipated risks associated with you taking part in this study, and you have full control over what information you provide. If you do wish to complain about any aspect of the way you have been approached or treated during the course of the study, you may address this to Professor Michael Murray at School of Psychology, Keele University, Staffordshire, ST5 5BG or 01782 733311, alternatively you can phone the Patient Advice and Liaison Service (PALS) at the University Hospital of North Staffordshire on 01782 676450.

MeMory-PaD

Will my answers be kept confidential?

Any information that you give during the interview, and your personal information will be kept completely confidential. All information will be anonymised through the use of a unique study code, instead of your name. This unique study code will be used when transcribing and analysing the interview. If any direct quotes are used in the publication of the findings from this study, the quote will be attributed to your study code, not your name. All data will be stored on a password protected laptop.

Who is organising the research?

Dr Simon Ellis, Consultant Neurologist, University Hospital of North Staffordshire; Ms Sharon Hurlstone, Research Nurse Specialist, University Hospital of North Staffordshire; Mr Tom Shepherd, PhD student, School of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University; Dr Keira Watts, Research and Development Facilitator, Research and Development Department, University Hospital of North Staffordshire and Professor Julius Sim, Statistician, Keele University, have organised the study.

Contact for further information

If you would like further information, please contact Mr Tom Shepherd on 01782 734246.

MeMory-PaD

University Hospital of North Staffordshire,
Neurology Research Unit,
First Floor, Block B,
Stoke on Trent,
ST4 6QG.
Tel: 01782 675391.

3rd December 2013

Caregiver Information Sheet

Title of Study: Medication MeMory in Parkinson's Disease: a Feasibility Study.

Investigators: Dr Simon Ellis, Ms Sharon Hurlstone, Mr Tom Shepherd, Professor Nicky Edelstyn, Dr Keira Watts, Professor Julius Sim.

Invitation

You are being invited to take part in a research study investigating the concerns carers/spouses/partners of people with Parkinson's have about their loved ones taking part in research studies. The study is being carried out by Dr Simon Ellis, Consultant Neurologist, University Hospital of North Staffordshire, Ms Sharon Hurlstone, Research Nurse, Department of Neurology, University Hospital of North Staffordshire with colleagues from Keele University, Mr Tom Shepherd and Professor Nicola Edelstyn. The study is part of Mr Tom Shepherd's PhD, which is a much wider project looking at how medication affects memory in Parkinson's Disease and is funded by the National Institute of Health Research's *Research for Patient Benefit* grant.

Before you decide whether to take part or not, it is important for you to understand why this research is being done and what it will involve. You may also wish to discuss the study with family members before deciding. If anything is unclear or you would like more information, our contact details are at the end of this leaflet, please don't hesitate to contact us.

MeMory-PaD

What is the study about?

There are many concerns that people may have about a spouse/partner with Parkinson's taking part in research. This study aims to explore these concerns by interviewing spouses/partners of people with Parkinson's who recently declined to take part in a clinical trial investigating how Parkinson's medication affects their memory. It is important that we find out what people's main concerns about research are so that they can be addressed when designing research in the future.

Why have I been invited to take part?

You have been invited to take part because your spouse/partner was recently invited to take part in a clinical trial investigating the effect how Parkinson's medication affects memory. As a spouse/partner you may have had concerns about the research too. The aim of this study is to explore those concerns, so that when we are developing Parkinson's research in the future we can be sure to accommodate the needs and concerns of a participant's carer, spouse or partner too.

Do I have to take part?

You are completely free to decide if you wish to take part or not. Please feel free to discuss any aspect of the research with us (contact details are at the end of this leaflet).

If you do decide to take part you will be asked to sign two forms, one which provides your consent to take part and the second to say you are happy for us to use anonymised direct quotes from your responses. Even after you have provided consent you have the right to withdraw at any point, without giving a reason. Whether you decide to take part or not will NOT affect your or your spouse/partner's current or future healthcare.

MeMory-PaD

What will happen if I take part?

If you wish to take part, you will be asked to take part in an interview at a time, date and location most convenient to you. The purpose of the interview will be to explore any concerns you had about the clinical trial your spouse/partner was recently invited to take part in. The interview will last approximately 30 minutes and will be recorded via an audio recorder, and transcribed at a later date. You may ask for the interview not to be recorded, or for the recorder to be turned off at any time without giving a reason. You may refuse to answer any question you do not want to answer during the interview.

What are the benefits of taking part?

There are no immediate benefits to you for taking part, however by highlighting the concerns you had about the research your spouse/partner was recently invited to take part in, we may be able to design studies that are more appealing to both patients and carer/family members in the future.

What if something goes wrong?

There are no anticipated risks associated with taking part in this study, and you have full control over what information you provide. If you do wish to complain about any aspect of the way you have been approached or treated during the course of the study, you may address this to Professor Michael Murray at School of Psychology, Keele University, Staffordshire, ST5 5BG or 01782 733311, alternatively you can phone the Patient Advice and Liaison Service (PALS) at the University Hospital of North Staffordshire on 01782 676450.

MeMory-PaD

Will my taking part be kept confidential?

Any information that you give during the interview, and your personal information will be kept completely confidential. All information will be anonymised through the use of a unique study code instead of your name. This unique study code will be used when transcribing and analysing the interview. If any direct quotes are used in the publication of the findings from this study, the quote will be attributed to your study code, not your name. All data will be stored on a password protected laptop.

Who is organising the research?

Dr Simon Ellis, Consultant Neurologist, University Hospital of North Staffordshire; Ms Sharon Hurlstone, Research Nurse Specialist, University Hospital of North Staffordshire; Mr Tom Shepherd, PhD student, School of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University; Dr Keira Watts, Research and Development Facilitator, Research and Development Department, University Hospital of North Staffordshire and Professor Julius Sim, Statistician, Keele University, have organised the study.

Contact for further information

If you would like further information, please contact Mr Tom Shepherd on 01782 734246.

Appendix Y

MeMory-PaD

University Hospital of North Staffordshire,
Neurology Research Unit,
First Floor, Block B,
Stoke on Trent,
ST4 6QG.
Tel: 01782 675391.

3rd December 2013

Consent Form (I)

Title of project: Medication and MeMory in Parkinson's Disease: a Feasibility Study

Investigators: Dr Simon Ellis, Ms Sharon Hurlstone, Mr Tom Shepherd, Professor Nicky Edelstyn, Dr Keira Watts, Professor Julius Sim.

Please read each of the following statements and initial the corresponding box if you agree.

1. I confirm that I have read and understand the information sheet (version 1.0) dated **3rd December 2013** for the above study and have had the opportunity to ask questions.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that data collected about me during this study will be anonymised before it is submitted for publication in scientific and medical journals, and presented at conferences.

☐

4. I agree to take part in the study

☐

5. If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analysis.

☐

6. I agree to be contacted about possible participation in future research projects.

☐

MeMory-PaD

Name of participant

Date

Signature

Name of researcher

Date

Signature

1 for participant, 1 for researcher.

Appendix Z

MeMory-PaD

University Hospital of North Staffordshire,
Neurology Research Unit,
First Floor, Block B,
Stoke on Trent,
ST4 6QG.
Tel: 01782 675391.

3rd December 2013

Consent Form (II)

Title of project: Medication and MeMory in Parkinson's Disease: a Feasibility Study

Investigators: Dr Simon Ellis, Ms Sharon Hurlstone, Mr Tom Shepherd, Professor Nicky Edelstyn, Dr Keira Watts, Professor Julius Sim.

Please read the following two statements and initial the appropriate box.

1. I **DO** agree to the use of anonymised direct quotes.

☐

2. I **DO NOT** agree to use of anonymised direct quotes.

☐

Name of participant

Date

Signature

Name of researcher

Date

Signature

1 for participant, 1 for researcher.

Appendix AA

I-Px5

Int: Okay, That's good. So, erm, did you understand what the trial was about. First of all.

Yes. Don't ask me!

Int: SO, do you know what the aims of the trial were?

I think so yeah. A long time ago so again, because it wasn't relevant to me, I didn't bother to pursue what it was about.

INT: Yeah. If it was more relevant to you-

Oh yeah, I would have looked at it then.

Int: Do you think that then you would have been more interested?

Yeah, it's because I couldn't take having time off one of the drugs. It just wasn't **feasible**.

Int: Right, so

It wasn't relevant to read it **almost**

Int: Yeah. Was the information we sent out clear/understandable? So could you glean from the information that we sent out enough to make-

Don't ask me that

Int: A, er, decision whether to take part

Well, that's too long for a **start**.

Int: You think it's too long?

Oh yeah

Int: Yeah

For the majority of people this is one of my **gripes**

Int:

Bullet points, A4 sheet, no **longer**.

Int: So, then. To make it-

Most people won't read that.

Int: Yeah. This is a really good point, this is really interesting. So, all the studies that we run have to go through an ethics-

Mmm

Commented [p1]: SWITCHING MEDICATION – risk to stability – not an option

Commented [p2]: SWITCHING MEDICATION – risk to stability – not an option

Commented [p3]: ACCESSIBILITY – PIS - too long

Commented [p4]: ACCESSIBILITY – PIS - too complex

Commented [p5]: ACCESSIBILITY – PIS - too long – suggests a summary

Int: committee. Erm, and before our information sheets are approved, they're checked by this ethics committee, and they have certain pre requisites about things that need to be included.

Yeah

Int: So, pretty much everything in there, has to be in there. What we could have done, are you saying that like perhaps, a summary sheet as well?

I think yeah. And then people can look at it further. I mean, that's my feeling. I mean, we've just had a erm sound equipment survey done at the church by experts, in inverted commas, and he's given it through, emailed it through and, I've said to one of the other guys. I said, 'It's too complicated'. People look at that, get lost in it all. So you want an A4 bullet point sheet- then if they want the full report, they can look at it. But the trouble is, if you have too much information, you just get lost in it.

Int: Yeah. Absolutely. It's a good point.

People don't read stuff

Int: No, no

You see how quick I read it

Int: So, perhaps then, an A4 sheet, bullet points, and then, something at the bottom which says, for more details, see the information.

Yeah, yeah.

Int: Okay.

That would be my preference. They need to know within the first, erm, page, erm, you know, what it's about and everything else.

Int: Yeah

Erm, and to grab their attention. Once you start sort of rambling on, erm. And I understand, you know, you've got to put so much in there. How you make it simple I don't know it's not an easy job. Erm, visualisation is good. Erm I'm very much one for sort of, erm, I mean. Again diagrams, pictures, good. But does everybody- do people follow flowcharts, and that.

Int: Yeah

I do, but that's my sort of-

Int: So do you think the flowcharts in there need to be made more simple as well?

Erm, I don't know really. I think it's simple enough isn't it? I think- the difficulty is, isn't it, you're tryna get across the whole thing to people, so therefore, you've got to have it in there. Erm. But this would bore me to tears really, this (laughs)

Int: Direct quote!

Sorry, I'm trying to be honest (laughing)

Commented [p6]: ACCESSIBILITY – PIS - too long – can get lost in it

Commented [p7]: Suggests summary first, then the PIS for more detail.

Commented [p8]: ACCESSIBILITY – PIS - Suggests people need want the first page to be more detailed with what will happen

Commented [p9]: ACCESSIBILITY – PIS - Suggests language is too complicated

Commented [p10]: ACCESSIBILITY – PIS - Suggest more pictures to make it more accessible.

Commented [p11]: ACCESSIBILITY – PIS - too - Suggests more flow diagrams

Commented [p12]: ACCESSIBILITY – PIS - too boring

Int: No not at all, that's what we want. We want you to be as honest and as frank as possible, because we don't want you to sugar-coat anything-

Yeah

Int: About this. Because that will lead us down, a bad road, maybe. In how we approach things,. What we want is you to be as honest with us as possible, because that's how we're gonna get to designing better information and-

I mean, it's not really a sort of related example but I've joined the PBG at the doctor's surgery.

Int: Yeah, yeah

And the first time I went along- because they have to do a survey every year. And, I see this survey and I thought, oh my goodness, who on earth would actually fill that in? And it was one of these ones when you sort of, have a long question, and then, sort of, different varieties of answers. Then another long question with a different way of answering the question. And, you just sort of throw it out the window, or doe of something, in-between. You know, if they condensed it down to one sheet, boxed it and everything else- you know- far easier to read, understand. And I think it is the way we sort of simplify things. We've got to understand that people are complete idiots.

Int: Yeah

Me included. Well if you make it too complicated, and I think of other people, erm, don't read things or don't understand things we complicate things, with words. And it's always a major issue as to how you get the information across and out.

Int: Yeah, yeah, okay. Thanks for that, that's really useful actually. Er, who would you prefer to contact you about taking part in research? And how would you prefer them to contact you?

I don't know who there is you're referring to that I could answer-

Int: So, okay, let me go through a couple of examples. It could be, your consultant, it could be any consultant, at er, UNHS. It could be the Parkinson's nurse. It could be lead researchers, so people who have the grants that pay for the research. It could be research nurse, cause at UNHS, they have- each department-

I don't think I have any preference. Erm, I do have a preference for people not ringing.

Int: Right.

Because, you never know who's actually ringing on the other end of the phone, so-

Int: Right.

Unless I know the person, I wouldn't want to give out information over the phone. Parkinson's, website, do send out a regular email for research, and there are things in there that you can give to different types of projects to sign up to and stuff. Which is quite a good way of keeping people informed.

Commented [p13]: NO preference on who makes the initial in relation to research.

Commented [p14]: Prefers NOT to be telephoned.

Commented [p15]: FEAR OF UNKNOWN – Research team - Doesn't want to give discuss information over the phone to someone

Commented [p16]: Email may be better.

Int: From a university, academic research, point of view though, would you prefer to be contacted by someone from the clinical team or the academics- so the consultants, or your personal consultant, the research nurse, or, the academics, the researchers, the postgraduates, that kind of thing. Does that matter?

No I don't think that matters, I mean, basically, if you're doing the research, then I would be happy for that contact to come from you.

Commented [p17]: No preference on who makes the initial contact though.

Int: Right okay.

Provided, that you're not bogus.

Commented [p18]: FEAR OF UNKNOWN – Research team Concern over identity of caller.

Int: Yeah. (laughs). So I was just thinking, obviously, you don't know me, but you know Dr Ellis-

Well, we'd had the information and it fitted. But I mean, if you'd just cold called and said I'm a researcher doing research into Parkinson's and things, I'd probably tell you to get lost, you know.

Commented [p19]: FEAR OF UNKNOWN – Research team It's important to have familiarity with the person, when approaching over the phone

Int: So therefore-

I mean, it's like you have these Microsoft people that- I lead them up the garden path.

Int: So, from your point of view then, familiarity with whoever's calling is very important?

Yeah, I think so. I knew where you were coming from, I knew about the research so I was happy to say yes. There's got to be that connection, not just a cold call.

Commented [p20]: Had familiarity with me.

Int: Okay, Okay. So, sort of coming from that, is there a preferred way for them to contact you, so for instance, you don't like it to be by the phone unless you're familiar with the person?

Well, emails good, but then you've got to have the email address in the first place haven't you? If it comes by post, it's probably going to be a long page thing like that which-

Commented [p21]: Written information through the post is preferred.

Int: Yeah, absolutely

I mean, I speed read so, I can get through it quite quick.

Int: Absolutely. So, change tact slightly, what does the term, clinical trial, mean to you?

I don't know I assume it to be more- sort of- well I suppose you think of drug trials, but whether that is correct, I don't know. But I suppose, I'd think of it like that- it's a trial using different- doing different things with different people, to see what the end result is.

Commented [p22]: Thinks drug trials with the term clinical trial

Int: yeah, yeah. And what kind of drugs do you associate with a clinical trial?

Well, it needn't necessarily be a drug, it could be an exercise- or something like that. I would assume it would be anything that relates to how a person reacts, I guess.

Commented [p23]: Good, accurate understating of the term clinical trial

Int: And, so, you don't then associate clinical trials with brand new drugs- drugs that have never been used before?

No, not really.

Commented [p24]: Doesn't associate clinical trials with new drugs.

Int: Okay, good. Have you ever participated in any research before?

Erm, only online.

Commented [p25]: Has participated in online research

Int: So, nothing to do with, like a clinical trial, or-

Well, I haven't really determined what a clinical trial is.

Int: Yeah, okay. So, research to do with anything- you've taken part in stuff online?

Well, Parkinson's online, they did a sort of, online survey, er, so that really wasn't a trial, no.

Commented [p26]: FEAR OF UNKNOWN – Research process - Online survey research, no trials though

Int: And what do you think of that- that kind of research?

Yeah it was good.

Int: What made it good, was it the fact that-

Well, I could do it fairly easily, and erm, being able to give information about where you're coming from, that is helpful, erm, building up different trials or whatever, I don't know.

Int: Yeah, yeah. Erm, have you ever discussed taking part in research with any of your doctors?

No.

Commented [p27]: FEAR OF UNKNOWN – Research process - Never discussed research participation with dr

Int: Okay, is that something you would like to do? Is it something that you think should be done?

Erm, I don't know, well obviously Dr Ellis is involved, erm but, our own doctor, well yes. We won't say anything on that one.

Commented [p28]: Not happy with own doctor

Int: Okay, okay. So, what were the main concerns you had about taking part in this trial?

I couldn't take the drug.

Commented [p29]: SWITCHING MEDICATION – previous switching experience -Bad experience previously, of one of the drugs

Int: You couldn't take the? Other? Okay that's fine. Were there any other concerns that you had about the trial, as you looked at it?

Well, no it was out of the window, because I couldn't take the drug so there was no point in even looking at it. Wouldn't waste my time reading the rest of it.

Commented [p30]: SWITCHING MEDICATION – A risk to stability - Drug switching was a serious concern – much more than anything else.

Int: Right, right. But now that you know, er, the trial, involves switching medication, testing your memory after you've taken the tablet and then after a period of withdrawal from each tablet. Does that represent any concerns to you- the number of trips to the hospital that kind of thing?

Erm, again there wasn't any relevance, so I didn't really think about it or look at what it involved. It just, sorry it's not doable.

Int: Yeah sure. Erm, when you think about trials in Parkinson's- I know in this trial you felt you'd have a reaction to one of them, but say that drug was not that drug and it was a different drug?

You'd do good as a politician.

Int: Thank you. I don't know whether to take that as a compliment or not actually!

No, like a news interviews, sort of, we'll ask you this question, but a different way round.

Int: Does switching your medication represent a concern for you?

Yeah. Because I think the first sort of, 18 months, were a struggle.

Int: First 18 months?

Felt like that, I don't know what it was but-

Int: Yeah, yeah.

You know getting it right. I mean, it's only the beginning of the year that I've began to feel on a stable level, so. No, I wouldn't want to change easily.

Int: Because you wouldn't want to go through that again, for another 18 months.

So anything involved changing drugs, I wouldn't get involved in.

Int: Yeah, yeah. Cause it's not worth the risk of er-

No, no. I mean, I've just had a tooth extracted, erm, I'd say, just, about 8 weeks ago. A week after, I got an infection in the socket, and it literally took me downhill and er went to the GP and er no comment. I brought my appointment forward with Dr Ellis because normally have a 6 month. Went to see him last week and he said yeah, it's a definite reaction to the infection. So he's now having to increase the tablets to get me back to a normal state, so you know, there are so many things it effects. So once you get on the even keel, I'm not gonna try and sort of rock the boat.

Int: Yeah, no absolutely. That makes sense.

So have I answered the question or are you gonna ask it again?

Int: Might ask you again later- no I'm joking. Erm could you describe the experience of switching medication? For me?

Horrible. I mean, no other word for it. And it takes so long to come off it- you're sort of 6 weeks down 6 weeks up. Erm, yeah, not nice.

Int: Yeah, were you experiencing side effects from the drugs or did you find it wasn't controlling your Parkinson's as well or?

It's the side effects I think. Just feeling unstable and everything else.

Int: Yeah, okay. Are you in control of taking your medication or is that something that's guided by a partner/wife?

When you say in control?

Int: Is it your responsibility?

Commented [p31]: SWITCHING MEDICATION – A risk to stability
- Took 18 months to get stable on current medication

Commented [p32]: SWITCHING MEDICATION – A risk to stability
- Only very recently began to feel stable on his medication.

Commented [p33]: Very reluctant to change drugs again.

Commented [p34]: SWITCHING MEDICATION – A risk to stability
Lots of other medical events have also had a knock on effect on the PD symptoms recently. Not worth risking the even keel

Commented [p35]: SWITCHING MEDICATION – Previous
Switching experience - has been horrendous

Commented [p36]: Experience of side effect

Commented [p37]: Felt unstable when switching previously
previously.

Er, the doctors at my doctor's surgery probably wouldn't say it was, Dr Ellis is always very good in suggesting usually what you take and trying to help you make your own decision- which I like. Erm, so am in control- I don't know.

Commented [p38]: Like s having a say in the medication that he takes.

Int: Is it your responsibility to take it everyday? Or-

Oh yes. I mean from that point of view.

Commented [p39]: Has responsibility of taking medication.

Int: Or are you reminded? 'Have you taken it? Are you going to take it? Have you forgotten to take it?'

Erm, my computer will put on a nice song. (plays song). People are sitting here at 9 o'clock at night and suddenly a song will start playing on my computer.

Commented [p40]: Has an alarm to remind him to take medication.

Int: Really?

Yeah.

Int: What, that reminds you to take your tablet? Serious?

Yeah

Int: Well, actually that's a good way of doing it, so-

Well actually 2 o'clock and 9 o'clock my computer goes off. It doesn't do the morning.

Int: So you've got like an alarm set, effectively, that reminds you to take it?

Yeah. Because I think it is this regular taking-

Commented [p41]: Alarm system works well as a reminder to take medication

Int: Yeah absolutely. So effectively, you are, you're in full control, really. It's your responsibility to make sure you've taken it. What I mean is your wife isn't there reminding you to take it every-

Oh, no no. She's supposed to sort of be there, she's a nurse as well so.

Commented [p42]: No burden on caregiver through participation expected

Int: Right, absolutely. And I think, er, you might have answered this already, but you'd say you were fairly stable on your current medication, would you say?

Er, no. Cause I've had this, I've only just started to, I've had to up the (sinimet) to try and bring me back to where I was. But, it's using the drugs that I'm on to try and do that.

Commented [p43]: Unstable recently.

Int: Yeah, I see that. So, as a part of the trial at the moment, we would test you on your medication, so after you've taken your tablets as normal, but to get the eff- but obviously what we get from that is the effect of the condition plus the medication, so to get the effect of just the condition, we have to test you off the medication, or in other words, after a period of withdrawal. How would you feel about that?

I wouldn't do it.

Commented [p44]: Wouldn't go through withdrawal period for OFF-medication session

Int: You wouldn't do it all? So, effectively, it would be like being tested after not having taken your tablets for a day, so your Parkinson's symptoms would be worse. You would be more Parkisonal as we would call it. How do you feel about that?

Well, it's a bit of a mystery to me, because, er, you take these slow release tablets through the day, and Dr Ellis says, and it's often two weeks before it takes effect! So, getting your head round that one is...why am I taking a slow release tablet. **Erm**, so, I don't know what would happen after one day of not taking it, probably sort of two weeks later I would have to tell you what the result of not taking it that one day is.

Commented [p45]: Find slow release medication difficult to understand.

Int: So, the drugs are operated on a half life, so rupinerol has a half life of er 8 hours, so we test people after a period of withdrawal, which is 4 half lives, so you wouldn't take a tablet the day before testing-

I wouldn't do it anyway I don't think, because again the issues I've had with it, I'm trying to sort of **keep**-

Commented [p46]: In trying to keep stable, wouldn't really want to do anything to medication regime

Int: Everything stable. Absolutely, completely understandable. **Erm**, if I was to approach you and say we've got this trial and we've got these memory tests and all that type of thing, is how difficult the tests might be a decider for you. In terms of deciding whether to take part in research, whether the tests might be too difficult and that type of thing.

Erm, don't think **so**.

Commented [p47]: Not concerned about any of the tests being too difficult

Int: No, not a concern that you wouldn't understand the tests or would do poorly on the tests, nothing like that?

Erm, no I don't think so.

Int: Okay. If you had of taken part, how do you think this would have influenced your wife's role as part of this care team, as a care giver. Would it of increased the amount of work that she would have to do?

Wouldn't have thought so.

Int: So it wouldn't have affected **it**?

Commented [p48]: Doesn't think caregiver workload would increase through him participating

Wouldn't have thought so, no. She's still gonna play the bowls.

Int: Okay. So, do you think the area that the study is investigating, so, memory and how drugs affect memory is an important area of research in Parkinsons?

Yeah I think so **yeah**.

Commented [p49]: Memory important topic of research

Int: Is memory something that you've had difficult experiences or changes with?

It's difficult to know what is old age and what is Parkinson's really. But having said that, even the last 6 weeks that I've been on this, downhill **thing**, I've known that it's harder, sometimes, getting the words. So, yeah that's Parkinson's, not old age or senior moments. And that's sort of remedied by the drugs that you're on, so yeah, the drugs can affect- or the illness can affect- but the drugs help to stabilise that.

Commented [p50]: Thinks the effect drugs have are really important to try and understand.

Int: Yeah, and you think that learning about how the drugs affect memory is an important area of research? Is it of any value?

Yeah I think so. I think anything is a value, it's what you hope to achieve from the end of it. I think people worry about memory don't they?

Commented [p51]: Recognises memory is something people worry about

Int: Absolutely.

You know when you get to sort of Alzheimer's, and things like this, it's a real sort of issue, a worry for people.

Int: Yeah. Definitely. I'm not sure you'll be able to answer this, but were you aware of the care team and the procedures we had in place if you had a problem during participation in the trial?

No.

Commented [p52]: UNKNOWN – Research process -No awareness of care team in place in case of feeling unwell during the trial.

Int: Okay. What do you think the benefits of participating in this trial could have been, if any?

I can't answer that, cause I don't know quite. One would hope, long term benefits for Parkinson's sufferers.

Commented [p53]: Not sure of what benefits participation has.

Int: In that case, why do you think some people have taken part? In the trial?

I would have said because anyone with an illness like Parkinson's, or any of these sort of long term illnesses, that you want to provide answers for the future generation even if you don't get it yourself, and you're part of doing that. I mean, that would be my take.

Commented [p54]: Other people may take part to help others, even if it doesn't benefit the individual.

Int: Yeah, absolutely. Do you think you'd have been able to get anything out of this trial, personally, if you'd have been able to take part? Apart from meeting me obviously.

Well, that's the highlight of the trial, isn't it.

Int: Haha, yeah, but do you think you'd have got anything else out of the trial for yourself personally?

I can't see what, erm, unless you'd have told me how good my memory was but, er no I don't.

Commented [p55]: Can't see the personal benefit of participating in this trial

Int: Is there anything else you'd like to say about the study in general?

No, apart from how nice you are, how pleasant you are, to put it on record.

Int: Thank you very much. Okay, thank you for taking part today, that concludes the interview, so if you have any questions, you can ask me them now?

No.

Int: Okay, thank you.

